Intravenous Amisulpride for the Prevention of Postoperative Nausea and Vomiting

Two Concurrent, Randomized, Double-blind, Placebo-controlled Trials

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ABSTRACT

Background: Two essentially identical, randomized, double-blind, placebo-controlled, parallel-group phase III studies evaluated the efficacy of intravenous amisulpride, a dopamine D_2/D_3 antagonist, in the prevention of postoperative nausea and vomiting in adult surgical patients.

Methods: Adult inpatients undergoing elective surgery during general anesthesia and having at least two of the four Apfel risk factors for postoperative nausea and vomiting were enrolled at 9 U.S. and 10 European sites. A single 5-mg dose of amisulpride or matching placebo was given at induction of anesthesia. The primary endpoint was complete response, defined as no vomiting/retching and no use of antiemetic rescue medication in the 24-h postoperative period. Nausea incidence was a secondary endpoint.

Results: Across the two studies, 689 patients were randomized and dosed with study medication, of whom 626 were evaluable per protocol. In the U.S. study, 46.9% (95% CI, 39.0 to 54.9) of patients achieved complete response in the amisulpride group compared to 33.8% (95% CI, 26.2 to 42.0) in the placebo group ($P = 0.026$). In the European study, complete response rates were 57.4% (95% CI, 49.2 to 65.3) for amisulpride and 46.6% (95% CI, 38.8 to 54.6) for placebo ($P = 0.070$). Nausea occurred less often in patients who received amisulpride than those who received placebo. There was no clinically significant difference in the safety profile of amisulpride and placebo; in particular, there were no differences in terms of QT prolongation, extrapyramidal side effects, or sedation.

Conclusions: One of the two trials demonstrated superiority, while pooling both in a *post hoc* change to the plan of analysis supported the hypothesis that amisulpride was safe and superior to placebo in reducing the incidence of postoperative nausea and vomiting in a population of adult inpatients at moderate to high risk of postoperative nausea and vomiting.
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POSTOPERATIVE nausea and vomiting (PONV) remains a common problem in surgical units. Even after two or three prophylactic antiemetic interventions, patients with all four of the Apfel risk factors for PONV have an estimated 30 to 40% chance of suffering PONV.[1] Although serious morbidity resulting from PONV is rare, it can, nonetheless, be very unpleasant for patients, can delay discharge and/or lead to readmission to hospital, and can add to healthcare costs. New antiemetics, ideally those suitable for combination with existing agents, are, therefore, needed and represent a major component of the generally accepted aim of enhanced recovery after surgery.

Up to 2001, the dopamine D_2 antagonist droperidol was one of the most popular choices for PONV prophylaxis because of its favorable efficacy profile, especially against

What We Already Know about This Topic

- Even after multiple prophylactic antiemetic interventions, postoperative nausea and vomiting remains a significant clinical issue in the postoperative setting
- The potent D_2 and D_3 antagonist amisulpride, a substituted benzamide, showed promising prophylactic antiemetic effects in a phase II dose-ranging study

What This Study Tells Us That Is New

- In two essentially identical, randomized, double-blind, placebo-controlled, parallel-group phase III studies performed in adult inpatients undergoing elective surgery during general anesthesia and having at least two of the four Apfel risk factors for postoperative nausea and vomiting, a single 5-mg dose of amisulpride was safe and superior to placebo in reducing the incidence of postoperative nausea and vomiting

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nausea, but in that year, it received a boxed warning from the U.S. Food and Drug Administration for QT-interval prolongation, leading to a major decline in use. An alternative D_2 antagonist without such a safety risk could be a valuable option in the management of PONV.

The potent D_2 and D_3 antagonist amisulpride, a substituted benzamide, showed promising data in a phase II dose-ranging study investigating single 1-, 5-, and 20-mg IV doses. Compared to placebo, the occurrence of PONV was significantly reduced by both the 5-mg and, to a lesser extent, 1-mg doses, with no significant difference in adverse events (AEs) between placebo and any of the amisulpride doses.[2]

Two trials of essentially identical design were, therefore, conducted to test the hypothesis that a single, preoperative 5 mg IV dose of amisulpride was more effective than placebo at preventing PONV in adult, surgical inpatients at moderate to high risk of PONV. Although a consensus guideline has identified a goal for multimodal PONV prophylaxis to become an integral part of anesthesia,[3] the clear demonstration of single-agent efficacy, especially in comparison to placebo, remains an essential first step in establishing the antiemetic potential of a new agent.

Materials and Methods

Study Design and Population

Two multicenter, double-blind, randomized, placebo-controlled, parallel-group studies involving patients at moderate to high risk of PONV undergoing elective surgery during general anesthesia were conducted concurrently between July 2013 and January 2014 at four sites in France and six in Germany (European study, registered at ClinicalTrials.gov, NCT01991821, on November 11, 2013; Chief Investigator: Dr. Pierre Diemunsch) and at nine sites in the United States (U.S. study, registered at ClinicalTrials.gov, NCT01991860, on November 11, 2013; Chief Investigator: Dr. Tong J Gan). An independent ethics committee approved the protocol at each institution, and written informed consent was obtained from all patients. The two study protocols were intentionally identical in all material respects, including design, subject inclusion/exclusion criteria, assessments, definition of key endpoints, and analysis populations. This was done to meet the requirement of drug regulatory agencies for data from at least two studies to support new drug approval. The data from these two trials are reported here individually; in addition, although not prespecified, a pooled analysis is also presented to obtain a study-adjusted estimate of treatment effect.

Subjects were eligible for inclusion if they were at least 18 yr of age; had given written, informed consent; had at least two of the four Apfel risk factors for PONV (history of PONV or motion sickness, habitual nonsmoking status, female sex, and expectation of receiving postoperative opioids for analgesia); were scheduled to undergo any elective surgery during general anesthesia; and were expected to last at least 1 h from induction of anesthesia to wound closure and requiring overnight hospitalization. Patients were ineligible if, among other things, they were scheduled for outpatient/ambulatory, intrathoracic, transplant, or central nervous system surgery; were expected to remain ventilated or need a naso- or orogastric tube *in situ* for a period after surgery; had a preexisting vestibular disorder or history of dizziness or preexisting nausea or vomiting in the 24 h before surgery; or were being treated with regular antiemetic therapy including systemic corticosteroids.

Study Medication and Anesthesia

Patients were screened up to 14 days before the planned date of their operation and admitted to hospital on the day before (day 1) or morning of their operation (day 0). The choice of anesthetic technique and drugs administered was at the discretion of the investigator, except that no antiemetic drug (other than the study drug) could be administered for any reason before or during the operation; no antiemetic could be administered postoperatively except as rescue medication; and the use of total IV anesthesia (TIVA) with propofol was not permitted although induction with propofol was allowed. Local and/or regional anesthesia was permitted in combination with the general anesthesia. Patients were randomly allocated on a 1:1 basis to receive a single IV dose of either 5 mg amisulpride or an identical placebo *via* a web-based randomization service, which automatically provided the next patient number from a predetermined randomization list created by an independent statistician. The list was stratified according to whether the patient had two, three, or four risk factors. Each subject number provided by the system matched a vial of study drug held at the study site, the identity of which was blinded to everyone except the contract manufacturer responsible for clinical packaging. The study drug was given by slow IV administration during 1 to 2 min at induction of anesthesia.

Study Assessments and Endpoints

Investigators recorded the occurrence and severity of any emesis or nausea within the 72-h period after completion of the operation. Emesis was either vomiting, defined as the

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production *via* the mouth of even the smallest amount of stomach contents, or retching, defined as the same muscular actions as vomiting but without expulsion of stomach contents, usually because of an empty stomach. Nausea was defined as the urge to vomit without the presence of expulsive muscular movements. The severity of nausea was measured using a patient-reported 11-point verbal rating scale, where 0 represented no nausea and 10 represented the worst nausea imaginable, a widely used instrument in PONV trials. A score of 4 or above was considered to represent "significant nausea."[4] Any spontaneous complaints of nausea by patients were noted and assessed for severity; in addition, patients were asked if they had nausea at 1, 2, 6, and 24 h after completion of surgery (wound closure) and, if so, to score it for severity. Additionally, any use of rescue antiemetic medication in the 72-h period was recorded. Rescue medication was to be given to any patient with emesis or with nausea from which they requested relief. The choice of rescue agent(s) was at the investigator's discretion. Patients could take home rescue antiemetics or a prescription on discharge. Patients given, postoperatively and before any episode of PONV, any drug considered to have clinically relevant antiemetic activity for reasons other than rescue, *e.g.*, an antihistamine for an allergic reaction, were excluded from the per-protocol (PP) analysis. A record was kept of all other medications taken between study entry and discharge.

Patients could be discharged from 16 h after completion of surgery, provided that they had completed an overnight stay and scheduled procedures were completed before discharge. Any patients who had not experienced PONV by the time of discharge were given a diary card to complete at home to capture any emesis, nausea, and rescue medication use up to 72 h after wound closure. Patients were followed up in person or (if discharged) by telephone at 72 h to ascertain if further episodes of PONV had occurred and, at day 7, to record any emergent AEs.

The primary endpoint was the composite measure complete response (CR), defined as no episodes of emesis (vomiting or retching) and no use of rescue medication in the first 24 h after wound closure, the opposite of which was defined as PONV. Secondary efficacy variables included the incidence of the individual parameters, emesis, significant nausea, any nausea, and use of rescue medication in the time periods 0 to 2, 0 to 6, 0 to 24, and 0 to 72 h after completion of surgery and the time to first occurrence of each variable. The safety and tolerability of amisulpride were assessed by recording AEs reported by patients or observed by site staff, by assessing vital signs and electrocardiograms at baseline and at 1 and 24 h after surgery, and through clinical hematology and biochemistry samples taken at baseline and at 24 h after surgery.

Statistical Analysis

Two efficacy populations were prespecified: an intention-to-treat (ITT) population, to include all patients who were randomized and received study medication, and a PP population, defined as the ITT population but excluding any patients who did not have an efficacy assessment documented at the nominal 24-h time point (unless they had already had an episode of PONV before that) and any patients with major protocol violations that could reasonably be considered to have had a material impact on the efficacy assessment, such as the inadvertent use of antiemetics, or on the baseline PONV risk, such as the use of TIVA or a surgical operation lasting less than 20 min. Safety data were analyzed on all patients who were randomized and received study medication. Inclusion of subjects into these populations was decided and documented before unblinding. A detailed policy regarding missing data was prespecified for both trials and signed off before unblinding; the incidence of missing data was in fact extremely low. Each study had a planned sample size of 170 subjects per arm in order to have a 95% power to detect a difference in CR rates of 60% in the amisulpride arm and 40% in the placebo arm at a two-sided significance level of 5%. All comparisons of event incidence between the study groups were tested using a Pearson chi-square test with Yates continuity correction. For time-to-event analyses, between-group differences were compared using a log-rank test. A *post hoc* analysis of pooled data from the two studies was conducted using a generalized linear model with binomial variance, identity link, and effects for study, treatment, and their interaction. This model was used both to estimate the treatment effect adjusted for study and to assess any difference in the treatment effect between the studies.

Results

In total, 689 subjects were randomized in the two studies and received active or placebo study treatment, 342 in the United States and 347 in Europe, of whom 626 were evaluable per protocol. Of the 63 subjects excluded from the PP population, all but one had either inadvertently received an antiemetic before, during, or after their operation, but before any event of PONV, or had a very short operation of 20 min or less. A Consolidated Standards of Reporting Trials diagram showing the disposition of patients is shown in figure 1, and the baseline characteristics of the PP populations are shown in table 1.[5]

The study arms were well balanced in terms of risk of PONV as estimated by prospectively ascertained risk factors. In both arms, a little more than a quarter of patients had two risk factors, just under half had three, and a quarter had all four. The range and duration of procedures were broadly similar between the arms and between the two studies, 50 to 60 of operations being abdominal procedures and the average duration being a little more than 2 h. The split between open and laparoscopic surgery was roughly even in the U.S. study, whereas open surgery predominated about 3:1 over laparoscopic surgery in the European study. Breast and axillary surgery was more common in the European study, while integumentary, musculoskeletal, and superficial procedures were common in the United States.

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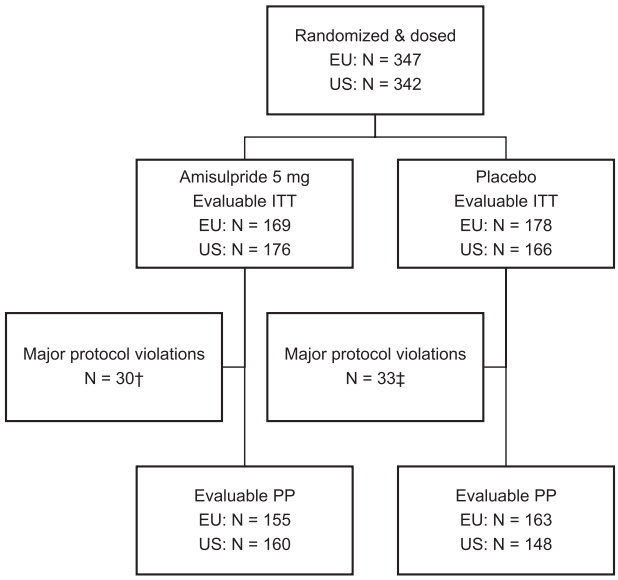

Fig. 1. Consolidated Standards of Reporting Trials diagram. †Violations: inappropriate antiemetic use (20 violations); operation duration less than 20 min (9 violations); and use of total intravenous anesthesia (1 violation). ‡Violations: inappropriate antiemetic use (22 violations); operation duration less than 20 min (11 violations). EU = European; ITT = intention to treat; PP = per protocol.

Rates in the PP populations of CR, emesis, nausea, and use of rescue medication for the two trials individually and on a pooled basis are presented in table 2. In the U.S. trial, there was a difference of 13.1% points (95% CI, 2.2 to 24.0) in the CR rate between the amisulpride and placebo groups, which was statistically significant ($P = 0.026$). In the European study, the difference in the CR rate was 10.8% points (95% CI, −0.1 to 21.7) and did not reach statistical significance ($P = 0.070$). On a pooled basis, the difference in the CR rate was 11.6% points (95% CI, 3.8 to 19.3; $P = 0.005$). After adjustment for study, the treatment effect remained statistically significant (11.9% points; 95% CI, 4.2 to 19.6; $P = 0.0025$), and there was no significant interaction between study and treatment effect (the treatment effect was 2.3% points higher in the U.S. study than in the European study; 95% CI, −13.1 to 17.7; $P = 0.77$). The relative reduction in the risk of PONV was very similar for the two studies (20.2% [95% CI, −0.4 to 37.1] in the European study and 19.8% [95% CI, 3.5 to 33.6] in the U.S. study).

Pooling the data from the two studies, the difference between amisulpride and placebo in terms of rescue medication use, significant nausea, and any nausea reached statistical significance ($P < 0.01$). Kaplan–Meier analysis of the time to first occurrence of PONV showed a separation of placebo and amisulpride curves within 1 to 2 h (fig. 2).

In the ITT population, results were similar to and consistent with those in the PP population: in the U.S. study, 44.3% (95% CI, 36.9 to 52.0) of patients achieved CR in the amisulpride group compared to 32.5% (95% CI, 25.5 to 40.2) in the placebo group ($P = 0.033$), and in the European study, 59.2% (95% CI, 51.4 to 66.7) achieved CR in the amisulpride group compared to 50.0% (95% CI, 42.4 to 57.6) in the placebo group ($P = 0.11$).

There was no difference in the incidence of treatment-emergent AEs (TEAEs) in the amisulpride group compared with the placebo group (table 3). There was one TEAE of life-threatening intensity (hemorrhage in a patient in the placebo group), and no fatal events occurred. The most frequent TEAEs were those to be expected in a surgical population and were similar in incidence in the two study arms, with the exception of elevated blood prolactin, which was seen in 7.8% of patients receiving amisulpride group compared to only 0.9% receiving placebo. However, although the median post-treatment prolactin level in amisulpride-treated patients was increased compared to the baseline level, it was still within the normal range for nonpregnant females, and no clinical events related to hyperprolactinemia were reported in either study.

There were no significant differences in electrocardiographic parameters between the groups in either study. The QT interval corrected for heart rate (QTc) at 1 h postoperatively was prolonged compared to baseline by on average 20.7 ms in the placebo group and 16.6 ms in the amisulpride group. At 24 h after the end of surgery, QTc had returned to its baseline average in both groups. There were no cardiac events judged possibly or probably related to study drug in either group nor any extrapyramidal side effects or sedation.

Discussion

These two concurrently run trials comparing amisulpride and placebo provide evidence that IV amisulpride at 5 mg is an effective antiemetic in patients undergoing surgery during general anesthesia, confirming previously reported findings.[2] A consistent relative risk reduction (RRR) of around 20% was seen in respect of the composite PONV measure, as well as for emesis, nausea, and requirement for rescue medication individually.

The two individual studies recruited a broadly similar, and clinically relevant, population of surgical patients at moderate-to-high risk of suffering PONV, with the average number of PONV risk factors per patient being 3. Based on validating studies of risk factors, which indicated a 20% PONV risk attributable to each risk factor, this would be predicted to give an baseline risk of PONV of around 60%.[6] This was indeed almost exactly the case across the pooled population, with the incidence of PONV in placebo group being 59.5%. Interestingly, though, the placebo PONV rate in the two individual trials differed considerably (53.4% in the European study; 66.2% in the U.S. study). This may be simply a result of random variation but might result, at least in part, from differential effects of major or minor risk factors or from differences in practice between Europe and the United States. For example, the proportion of patients with a history of PONV or motion sickness was somewhat lower in the placebo group of the European study than the U.S. study, which might contribute to a lower baseline risk.

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Table 1. Baseline Characteristics (Per-protocol Population)

	European Study		U.S. Study		Pooled	
	Amisulpride (n = 155)	Placebo (n = 163)	Amisulpride (n = 160)	Placebo (n = 148)	Amisulpride (n = 315)	Placebo (n = 311)
Age, yr						
Median	50	53	54	54	52	53
Range	19–83	18–83	23–88	21–86	19–88	18–86
Body mass index, kg/m^2						
Median	25.3	25.4	31.2	31.7	27.5	27.8
Range	17.6–42.0	16.6–48.1	16.2–62.1	17.3–66.2	16.2–62.1	16.6–66.2
Race, n (%)						
White/Caucasian	113 (72.9)	123 (75.5)	142 (88.8)	124 (83.8)	255 (81.0)	247 (79.4)
Other/unknown	42 (27.1)	40 (24.5)	18 (11.3)	24 (16.2)	60 (19.0)	64 (20.6)
Sex, n (%)						
Male	21 (13.5)	22 (13.5)	58 (36.3)	48 (32.4)	79 (25.1)	70 (22.5)
Female	134 (86.5)	141 (86.5)	102 (63.8)	100 (67.6)	236 (74.9)	241 (77.5)
History of PONV/motion sickness, n (%)	64 (41.3)	55 (33.7)	67 (41.9)	58 (39.2)	131 (41.6)	113 (36.3)
Nonsmoker, n (%)	124 (80.0)	136 (83.4)	137 (85.6)	126 (85.1)	261 (82.9)	262 (84.2)
Expected use of postoperative opioids, n (%)	147 (94.8)	153 (93.9)	160 (100.0)	148 (100.0)	307 (97.5)	301 (96.8)
2 risk factors, n (%)	38 (24.5)	46 (28.2)	50 (31.3)	43 (29.1)	88 (27.9)	89 (28.6)
3 risk factors, n (%)	75 (48.4)	75 (46.0)	74 (46.3)	73 (49.3)	149 (47.3)	148 (47.6)
4 risk factors, n (%)	42 (27.1)	42 (25.8)	36 (22.5)	32 (21.6)	78 (24.8)	74 (23.8)
Surgical technique, n (%)						
Laparoscopic	49 (31.6)	44 (27.0)	71 (44.4)	71 (48.0)	120 (38.1)	115 (37)
Open	97 (62.6)	117 (71.8)	89 (55.6)	77 (52.0)	186 (59)	194 (62.4)
Surgical procedure classification, n (%)						
Abdominal	82 (52.9)	83 (50.9)	95 (59.4)	94 (63.5)	177 (56.2)	177 (56.9)
Breast, axilla	32 (20.6)	43 (26.4)	0	1 (0.7)	32 (10.2)	44 (14.1)
Endoscopy	25 (16.1)	18 (11.0)	3 (1.9)	2 (1.4)	28 (8.9)	20 (6.4)
Head, neck	8 (5.2)	11 (6.7)	1 (0.6)	1 (0.7)	9 (2.9)	12 (3.9)
Integumentary, musculoskeletal, superficial	8 (5.2)	7 (4.3)	61 (38.1)	50 (33.8)	69 (21.9)	57 (18.3)
Duration of surgery, min						
Mean	115.7	125.4	138.1	144.3	127.0	133.4
SD	76.6	86.0	81.6	74.4	79.8	81.2

PONV = postoperative nausea and vomiting analysis.

Table 2. Efficacy Data (Per-protocol Population)

	European Study			U.S. Study			Pooled		
	Amisulpride (n = 155)	Placebo (n = 163)		Amisulpride (n = 160)	Placebo (n = 148)		Amisulpride (n = 315)	Placebo (n = 311)	
	n (%)	n (%)	*P* Value	n (%)	n (%)	*P* Value	n (%)	n (%)	*P* Value*
CR, 0–24 h, 95% CI	89 (57.4), 49.2–65.3	76 (46.6), 38.8–54.6	0.070	75 (46.9), 39.0–54.9	50 (33.8), 26.2–42.0	0.026	164 (52.1), 46.4–57.7	126 (40.5), 35.0–46.2	0.005
CR, 0–72 h	84 (54.2)	68 (41.7)	0.035	67 (41.9)	46 (31.1)	0.065	151 (47.9)	114 (36.7)	0.006
Emesis, 0–24 h	34 (21.9)	45 (27.6)	0.299	34 (21.3)	36 (24.3)	0.610	68 (21.6)	81 (26.0)	0.224
Significant nausea, 0–24 h	62 (40.0)	83 (50.9)	0.066	69 (43.1)	82 (55.4)	0.041	131 (41.6)	165 (53.1)	0.005
Any nausea, 0–24 h	73 (47.1)	95 (58.3)	0.059	91 (56.9)	100 (67.6)	0.070	164 (52.1)	195 (62.7)	0.009
Rescue medication use, 0–24 h	59 (38.1)	80 (49.1)	0.062	83 (51.9)	97 (65.5)	0.021	142 (45.1)	177 (56.9)	0.004

*Unadjusted.

CR = complete response (no vomiting/retching and no use of rescue medication).

On the other hand, the U.S. study population included a higher proportion of male patients than the European study population, which might be expected to result in a lower, not higher, baseline PONV rate in the U.S. study. The proportion of nonsmokers and subjects expected to receive postoperative opioids was similar across the studies. Younger age

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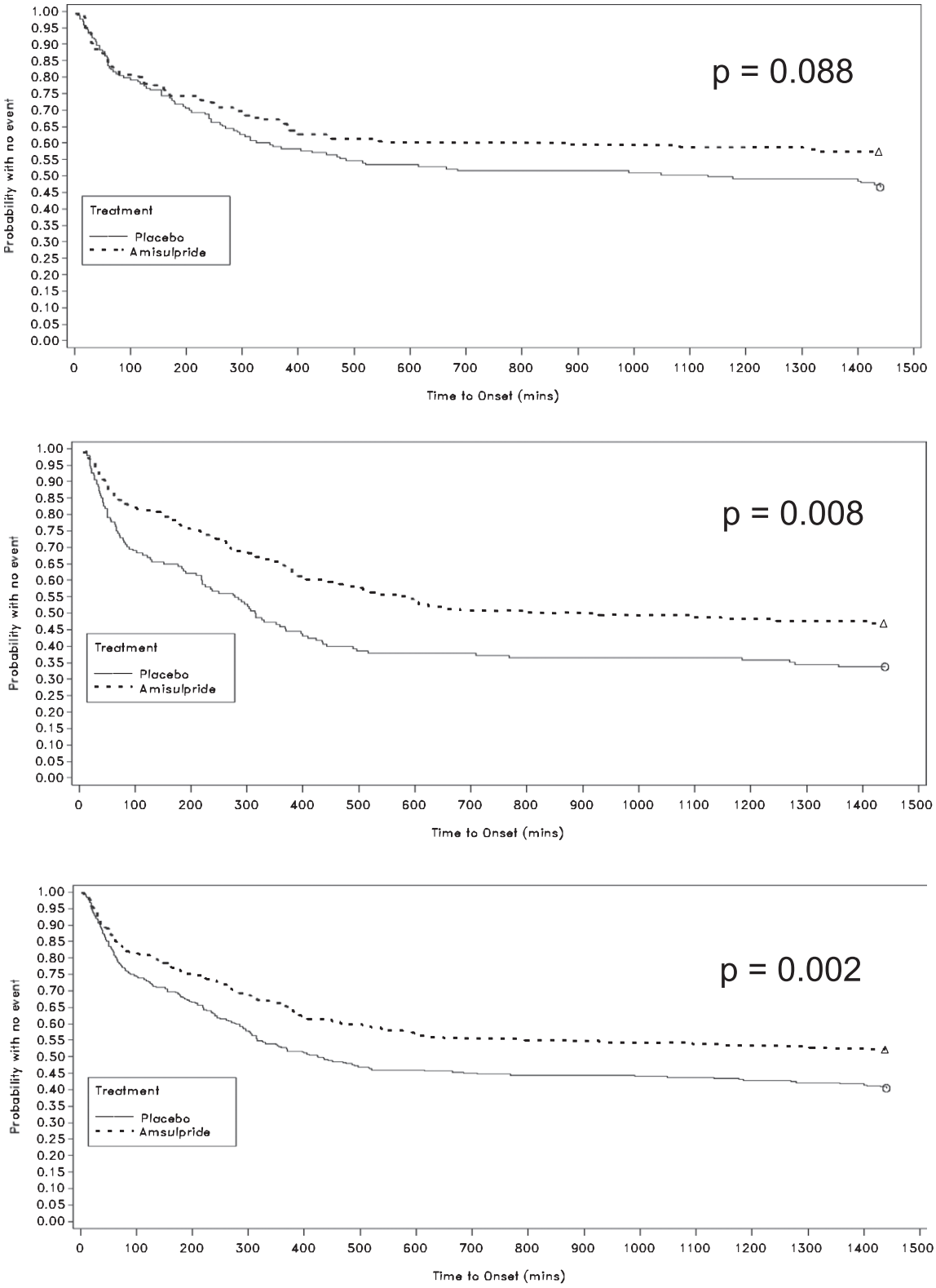

Fig. 2. Time to postoperative nausea and vomiting analysis. European study (A), U.S. study (B), and pooled data (C).

has been associated with a higher risk of PONV, but the age distribution was similar between the studies. The mean operation duration was some 20 min or 17% longer in the U.S. study, which is likely to have led to a greater exposure to volatile anesthetics. There was a difference in mean body mass index, but that has not previously been identified as

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Table 3. Incidence of Treatment-emergent Adverse Events

	Placebo (n = 344)	Amisulpride (n = 345)
	n (%)	n (%)
No. of patients with at least one TEAE	243 (70.6)	243 (70.4)
No. of patients reporting TEAE of life-threatening intensity	1 (0.3)	0
No. of patients reporting serious TEAE	9 (2.6)	9 (2.6)
No. of TEAEs leading to death	0	0
Frequent TEAE (≥ 5% incidence in either arm)		
Procedural pain	133 (38.7)	133 (38.6)
Hyperglycemia	38 (11.0)	33 (9.6)
Anemia postoperative	33 (9.6)	31 (9.0)
Hypocalcemia	30 (8.7)	30 (8.7)
Constipation	24 (7.0)	28 (8.1)
Blood prolactin increased	3 (0.9)	27 (7.8)
Hypoproteinemia	26 (7.6)	27 (7.8)
Leukocytosis	23 (6.7)	26 (7.5)
Flatulence	21 (6.1)	26 (7.5)
Nausea	21 (6.1)	25 (7.2)
Hypotension	24 (7.0)	18 (5.2)
Anemia	18 (5.2)	22 (6.4)
Pruritus	16 (4.7)	19 (5.5)
Abdominal distension	11 (3.2)	18 (5.2)
Headache	12 (3.5)	18 (5.2)

TEAE = treatment emergent adverse event.

a PONV risk factor. A wide range of operation types was seen in both studies, with the most notable differences in the overall pattern being more integumentary, musculoskeletal, and superficial procedures in the U.S. study and more breast and axillary surgery in the European study.

The main consequence of the surprisingly low placebo PONV rate in the European study is that the 20% benefit of amisulpride in terms of RRR translated into an absolute difference, which narrowly failed to reach statistical significance, whereas the same RRR seen in the U.S. study did translate into a statistically significant absolute benefit. Both studies were powered to detect a difference in the CR rate of 20 percentage points between active and placebo, partly because of the effect size seen in phase II,[2] and it is, therefore, unsurprising that they were underpowered in the context of a difference closer to ten percentage points. Pooling the data from the two studies increases the power markedly and is not unreasonable, given the essentially identical protocols. However, this was not prespecified, which clearly weakens any conclusions that can be derived from it.

Dopamine D_2 antagonists such as droperidol have previously been noted to be better against nausea than vomiting.[7] This was supported by this pair of studies, in which the RRR for nausea was generally better than that for vomiting/retching. This may reflect binding of the amisulpride to D_2 (and possibly D_3) receptors in the area postrema and elsewhere in the medulla, which are specifically involved in mediating the nausea response.[8] The role of D_3 receptors in human emesis is unknown. There is some evidence for their involvement in animal models,[9,10] but, apart from amisulpride, no clinically effective antiemetic agents have significant potency at the D_3 receptor. It remains to be seen if D_3 antagonism contributes sufficient antiemetic activity for amisulpride to add efficacy to another D_2-antagonist or to be effective as rescue therapy when another D_2-antagonist has failed.

The suggestion of predominantly antinausea efficacy for amisulpride may offer potentially important benefits in the clinical management of PONV. Consensus guidelines recommend that patients at higher risk of PONV are managed using a multimodal approach, including prophylaxis with a combination of antiemetic agents from different classes, as well as nonpharmacologic therapies and interventions that reduce baseline risk.[3] Large studies support the value of combination pharmacotherapy.[1] Typically, $5HT_3$ inhibitors and the corticosteroid dexamethasone are the mainstay of prevention nowadays. Droperidol was formerly considered by experts to be the drug of choice in PONV prophylaxis[7] because of its general efficacy and particular benefit in respect of nausea. The imposition of the boxed warning by Food and Drug Administration due to the risk of torsade de pointes has resulted in widespread abandonment of droperidol by surgical units in the United States,[11] leaving an important unmet need in PONV management.

In addition to its efficacy, amisulpride may have an appropriate pharmacologic and safety profile for use in combination with other antiemetics. It has limited metabolism[12]; neither induces nor inhibits liver enzymes[13]; exhibits limited plasma protein binding[14] so does not displace other drugs from plasma proteins; and has no drug interactions of note.[15] Its safety profile in psychiatric patients, in whom much higher doses, between 50 and 1,200 mg per day, are employed, often during prolonged periods, has been indistinguishable from placebo in clinical studies and postmarketing surveillance since its launch 30 years ago.[16,17]

These studies confirm that benign safety profile; in particular, toxicities of concern typically associated with dopamine antagonists were not seen. There were no spontaneously reported extrapyramidal signs—although specific monitoring, for example, using the Barnes akathisia scale, would be helpful to be more confident about the absence of extrapyramidal sign liability—and there was no difference in mean change in QTc interval between the amisulpride and placebo arms nor any study drug–related cardiac adverse reactions.

The only AE that occurred more frequently with amisulpride than placebo was increased serum prolactin, a well-documented and understood effect of dopamine antagonists, especially at lower doses, caused by their stimulation of prolactin release from the anterior pituitary.[18] However, the clinical significance appears to be negligible, especially in the context of a single-dose treatment, since the increase was small—the posttreatment mean level not exceeding the normal range for nonpregnant females—and no clinical sequelae were reported.

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An important limitation is that although the population studied in these trials was typical of that included in PONV trials and indeed that most likely to be considered for PONV prophylaxis, it does not represent the generality of surgical patients, and the results may not be applicable to other important groups, such as ambulatory patients, those at low risk of suffering PONV, especially male patients, and those receiving TIVA. A further limitation is the absence of detailed data on patients' postoperative opioid consumption.

In summary, low-dose, IV amisulpride is an effective antiemetic, reducing the incidence of PONV in moderate- and high-risk patients undergoing surgery during general anesthesia, making it a potentially valuable addition to the therapeutic options available in the management of PONV.

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Competing Interests

Dr. Kranke serves as consultant for Acacia Pharma Ltd, Cambridge, United Kingdom. Dr. Leiman serves as speaker for Pacira (Parsippany, New Jersey) and Merck (Kenilworth, New Jersey) and consultant for Pacira, Durect (Cupertino, California), and Innocoll (Athlone, Ireland). Dr. Diemunsch received grant support from Ambu (Copenhagen, Denmark) and Takeda (Paris, France). Dr. Fox is an employee and stockholder of Acacia Pharma Ltd, Cambridge, United Kingdom. The other authors declare no competing interests.

Reproducible Science

Full protocol available from Dr. Fox: gabrielfox@acaciapharma.com. Raw data available from Dr. Fox: gabrielfox@acaciapharma.com.

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