Comparison of vestipitant with ondansetron for the treatment of breakthrough postoperative nausea and vomiting after failed prophylaxis with ondansetron

P. Kranke[1]*, J. P. Thompson[2], P. L. Dalby[3], L. H. Eberhart[4], E. Novikova[5], B. M. Johnson[6], S. F. Russ[6], R. Noble[7] and R. A. Brigandi[7]

[1] Department of Anaesthesia and Critical Care, University Hospitals of Würzburg, Oberdürrbacher Str. 6, D-97080 Würzburg, Germany
[2] Department of Anaesthetics, Leicester Royal Infirmary, Leicester, UK
[3] Department of Anesthesia, Magee-Women's Hospital, Pittsburgh, PA, USA
[4] Department of Anaesthesiology and Critical Care Medicine, Philipps-University, Marburg, Germany
[5] Department of Gynecology, Moscow Herzen Oncology Institute, Moscow, Russian Federation
[6] GlaxoSmithKline, Research Triangle Park, NC, USA
[7] King of Prussia, PA, USA

* Corresponding author. E-mail: kranke_p@ukw.de

Editor's key points

- This study found no difference between vestipitant and ondansetron when given after operation in surgical patients with postoperative nausea and vomiting after failed ondansetron prophylaxis.
- Vestipitant was superior to ondansetron in decreasing the episodes of postoperative emesis and retching.
- Safety profile of vestipitant and ondansetron was similar as recorded by adverse events.

Background. Postoperative nausea and vomiting (PONV) is common; ondansetron is often used as prophylaxis or for breakthrough episodes. Vestipitant is a neurokinin 1 (NK-1) receptor antagonist that is effective for prophylaxis, but its efficacy for treating established PONV is unknown. This study was performed to evaluate the efficacy and safety of vestipitant, compared with ondansetron for the treatment of breakthrough PONV in patients who had already received prophylactic ondansetron before surgery.

Methods. A multicentre, randomized, single-blind (sponsor-open), parallel group study. Of 527 surgical patients, 130 (25%) had breakthrough PONV and were equally randomized to one of six i.v. doses of vestipitant (4–36 mg) or ondansetron 4 mg. The primary endpoint was the rate of patients exhibiting complete response, defined as no emesis and no further rescue medication from 10 min after infusion up to 24 h after surgery or hospital discharge.

Results. All doses of vestipitant were non-inferior to ondansetron in treating PONV after failed prophylaxis with ondansetron. However, vestipitant was superior to ondansetron in decreasing episodes of postoperative emesis and retching. The complete response rate analysis using Bayesian model averaging indicated that no vestipitant dose was superior to ondansetron. Nausea numerical rating scale scores and the times-to-PONV or discharge were similar between the vestipitant and ondansetron treatment groups.

Conclusions. Although overall efficacy was non-inferior between vestipitant and ondansetron, the rate of emesis was lower with vestipitant. These data suggest that vestipitant may be a useful agent for the management of PONV, similar to other NK-1 antagonists.

Clinical trial registration. NCT01507194.

Keywords: nausea; neurokinin receptor antagonists; ondansetron; postoperative; vomiting

Accepted for publication: 18 September 2014

Postoperative nausea and vomiting (PONV) is the most frequently reported patient complaint after anaesthesia.[1–3] Ondansetron, a 5-hydroxytryptamine 3 (5-HT$_3$) receptor antagonist, is frequently used for the treatment of breakthrough PONV,[4–6] even in the setting of failed ondansetron prophylaxis.[7] Previous studies have demonstrated that re-treatment with the same class of drug is often unsuccessful if the first dose was ineffective.[8 9] Studies in patients who experience PONV after prophylaxis with 5-HT$_3$ antagonists have shown that further treatment with ondansetron or other 5-HT$_3$ antagonists is effective in only 30–50% of patients.[7 9–11] Therefore, there is a clinical need for more effective treatment modalities for the rapid treatment of breakthrough PONV.

Vestipitant is a potent and selective neurokinin 1 (NK-1) receptor antagonist. Further to indications of depression, functional dyspnoea, anxiety, insomnia, irritable bowel disease, gastrooesophageal reflux disease, and tinnitus, vestipitant is currently being investigated for its antiemetic potential. In a

previous study, oral vestipitant 25 mg in combination with ondansetron 4 mg i.v. was more effective in the prevention of PONV compared with ondansetron alone (60% and 42%, respectively) (unpublished data; NCT00600990). In the same study, vestipitant 18 mg i.v. in combination with ondansetron 4 mg i.v. resulted in a greater complete response rate (55%) in the prevention of PONV when compared with ondansetron alone (42%), although this difference was not statistically significant (97.5% CI: 0.98–2.75). The oral and i.v. doses of vestipitant used in that study resulted in comparable plasma levels of vestipitant, although the i.v. vestipitant formulation was mannitol-based and required infusion of >15 min. While the oral route or a slow infusion may be suitable for prophylaxis, rescue therapy for established PONV needs a more rapid infusion to achieve rapid therapeutic effects exposure. These limitations would limit the utility of the currently available NK1 inhibitors aprepitant (oral) and fosaprepitant (slow i.v. infusion). In order to have the ability to rapidly infuse vestipitant and to reduce the potential for haemolysis, a formulation of vestipitant containing sulfobutylether-7-β-cyclodextrin (SBE7-β-cyclodextrin, Captisol™) was developed. This was shown to be safe and well tolerated, with no evidence of haemolytic activity at total doses of 12–48 mg administered in ≤2 min in healthy subjects.[12]

The primary aim of this study was to evaluate the efficacy, safety, and tolerability of the new Captisol™ vestipitant i.v. formulation of vestipitant compared with a standard i.v. dose of ondansetron 4 mg for the treatment of breakthrough PONV, after a failed prophylaxis regimen that included i.v. ondansetron 4 mg before surgery.

Methods

This study was conducted according to the ethical principles of good clinical practice (GCP) and the Declaration of Helsinki. The protocol and amendments were all approved by the local institutional review board (IRB) or research ethics committees, and the trial was registered at http://clinicaltrials.gov (NCT01507194). Written informed consent was obtained from all patients before surgery.

Inclusion

Patients (aged 18–75 yr, ASA physical status I–II), with multiple risk factors for PONV and undergoing non-emergency surgery lasting >40 min under general anaesthesia, were enrolled as potential participants into the study. All patients had three or more of the following risk factors for PONV: (i) female gender, (ii) non-smoker in the last 6 months, (iii) history of PONV or motion sickness, or (iv) planned postoperative opioids. All types of surgical procedures were permitted except those for laparoscopic biopsies and cardiac/cardiothoracic surgeries. All patients received prophylactic antiemetics according to institutional practice, and including ondansetron 4 mg i.v. but not an NK-1 inhibitor (aprepitant or fosaprepitant). Only those who experienced vomiting, persistent nausea, or the need for an antiemetic (on patient request)

through 4 h after emerging from anaesthesia were eligible for enrolment.

Study design

This was a multicentre, randomized, double-blind (sponsor unblind), active controlled, parallel group study performed at 38 sites in six countries. Eligible patients were equally randomized to receive a single dose of one of six treatments: vestipitant (4, 6, 12, 18, 24, or 36 mg i.v.) or ondansetron 4 mg i.v. Patients were randomized to their treatment assignment before surgery, so that the i.v. medication could be prepared in advance and ready to be administered after surgery, if needed. After surgery, patients who experienced breakthrough PONV received randomized dose of medication in a single-blind manner (patients and study staff were blinded, unblinded to sponsor and those who prepared or administered the dose).

General anaesthesia was induced and maintained according to standard regimens at each institution. As a study requirement, all surgeries involved ≥40 min of anaesthesia. The start of anaesthesia was the time of administration of the first anaesthetic agent and the end was the time of extubation or equivalent. The use of neuraxial anaesthesia, total i.v. anaesthesia, and propofol for maintenance of anaesthesia were prohibited (propofol was allowed for induction of anaesthesia). Total i.v. anaesthesia was not allowed in this study. Efforts were made to maintain consistent subsequent analgesia for each patient. Administration of any medication through the use of an epidural catheter was not permitted. The use of patient-controlled administration (PCA) devices was permitted. Local anaesthetic infusions were allowed as long as they were being used in addition to the anticipated use of systemic opioids. Postoperative use of nasogastric or oral gastric tubes was also prohibited.

Efficacy was evaluated by several means including assessment of nausea by a verbal rating scale, occurrence of breakthrough PONV, time to occurrence of PONV, and readiness for discharge from the hospital from a PONV perspective. The nausea numerical rating scale (NNRS) was a verbal rating scale where the subject was asked to rate the severity of nausea between 0 and 10 with 0 being no nausea and 10 being the worst possible nausea. Breakthrough PONV was defined as one of the following: postoperative nausea score of ≥7 on the NNRS, or nausea resulting in a subject requesting an antiemetic, or an episode of emesis or retching. Time to PONV or discharge readiness was defined as the following: when, disregarding all other considerations, the subject had no PONV that would prevent the subject from being discharged from the hospital or clinic.

The primary safety and tolerability endpoints were adverse events (AEs) and serious adverse events (SAEs) observation and safety laboratory evaluations. Data were entered securely into an electronic data collection system.

Venous blood samples (2 ml) for pharmacokinetic (PK) analysis of vestipitant were obtained at 2, 15 min, 1, and 6 h post-dose. If not discharged from hospital, further samples were obtained at 12 and 24 h post-dose, or immediately before discharge if more than 4 h had elapsed from the last PK sample.

Human plasma samples were analysed for vestipitant using a validated analytical method based on protein precipitation, followed by ultra high pressure liquid chromatography tandem mass spectroscopy (UHPLC-MS-MS) analysis. Using a 50 μl aliquot of human plasma, the lower limit of quantification for vestipitant was 1 ng ml^{-1} and the higher limit of quantification was 2000 ng ml^{-1}.

Statistical analysis

The primary endpoint for efficacy in this study was the number of patients achieving a complete response after receiving study medication to treat breakthrough PONV. The programmatic objective was to identify at least one dose of vestipitant that exceeded the complete response performance rate of ondansetron by 20% with a posterior probability of >0.900 (calculated to three decimal places). An interim analysis was incorporated for the study to progress only if at least one dose of vestipitant had a posterior probability >0.300 with its complete response rate exceeding that of ondansetron by 20%.[13] The period for the primary efficacy endpoint began 10 min after the infusion end. Complete response was defined as no emesis and no further rescue medication from 10 min after infusion end up to 24 h after surgery, or hospital discharge, whichever was sooner.

Bayesian model averaging was utilized across the five vestipitant dose results to create a response curve with multiple models providing weighted contributions. The response curve was compared with ondansetron data which were augmented by an informed prior. The Bayesian model averaging approach combined with the comparator-informed prior reduced the overall sample size and provided >80% power to observe any dose being at least 20% better than the control. Data were analysed using SAS 9.2 (SAS Institute Inc., 100 SAS Campus Drive, Cary, NC, USA).

PK data were analysed using standard non-compartmental methods and descriptively summarized (WinNonlin Enterprise v5.2, Pharsight Corp., Sunnyvale, CA, USA). Dose proportionality of selected PK parameters was assessed using a power model ($Y = \alpha \times \text{Dose}^{\beta}$, where β represents the estimated slope) after log–log transformation.[14]

Results

A total of 527 patients were randomized before scheduled surgery; of which, 130 (25%) experienced breakthrough PONV and became eligible to receive the study medications (Table 1, Fig. 1). The proportion of subjects completing the study as planned per treatment arms ranged from 88% to 96% with an overall average of 93%, with no patient being withdrawn due to AEs.

Complete response, defined as no emesis and no further rescue medication from 10 min after infusion end up to 24 h or discharge from the hospital or clinic, was achieved in the majority of patients (56%) in the total population of patients treated with vestipitant compared with 42% in the ondansetron group (Table 2). The only vestipitant dose group which had a lower complete response rate than the ondansetron group was the vestipitant 18 mg group with a complete

Table 1 Patient characteristics

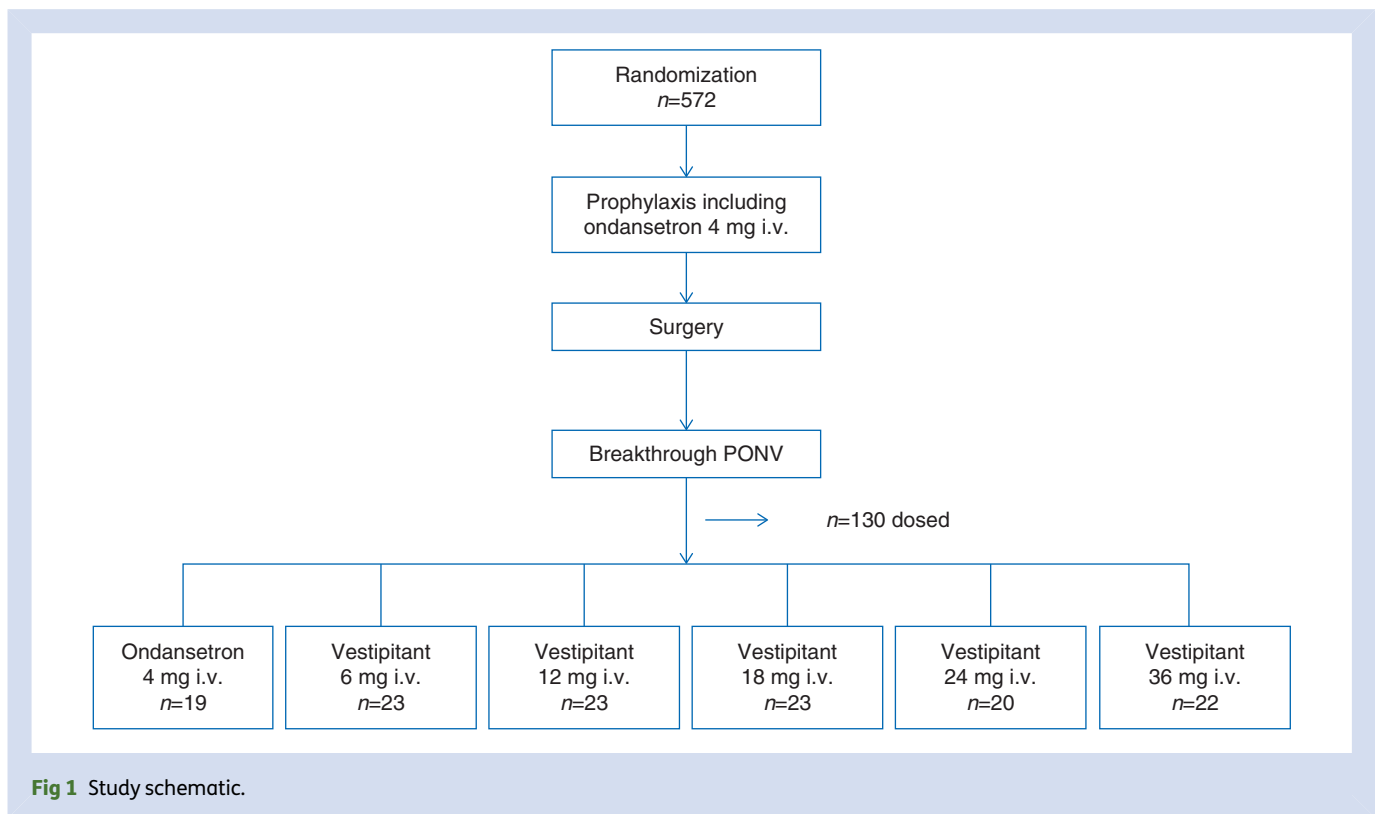|	Ondansetron	Vestipitant					Total (n=130)
	4 mg (n=19)	6 mg (n=23)	12 mg (n=23)	18 mg (n=23)	24 mg (n=20)	36 mg (n=22)	
Age (yr)							
Mean (range)	45 (20–73)	47 (31–71)	47 (23–73)	46 (21–70)	41 (19–63)	46 (25–65)	45 (19–73)
Age categorization [n (%)]							
<65 yr	17 (89.5)	21 (91.3)	22 (95.7)	21 (91.3)	20 (100.0)	21 (95.5)	122 (93.8)
≥65 yr	2 (10.5)	2 (8.7)	1 (4.3)	2 (8.7)	0 (0.0)	1 (4.5)	8 (6.2)
Gender [n (%)]							
Male	0	0	1 (4.3)	2 (8.7)	1 (5.0)	2 (9.1)	6 (4.6)
Female	19 (100.0)	23 (100.0)	22 (95.7)	21 (91.3)	19 (95.0)	20 (90.9)	124 (95.4)
Race [n (%)]							
White	17 (89.5)	22 (95.7)	21 (91.3)	22 (95.7)	19 (95.0)	22 (100.0)	123 (94.6)
Black or African American	2 (10.5)	0	2 (8.7)	1 (4.3)	1 (5.0)	0	6 (4.6)
Other	0	1 (4.3)	0	0	0	0	1 (0.8)
Weight (kg)							
Mean (SD)	83.0 (27.7)	70.4 (14.4)	75.4 (19.5)	77.6 (15.2)	72.6 (14.6)	82.0 (17.9)	76.7 (18.7)
Height (cm)							
Mean (SD)	158.2 (23.0)	163.3 (5.3)	167.2 (6.2)	165.8 (7.4)	165.4 (6.3)	167.2 (7.7)	164.7 (10. 9)
Geographic region [n (%)]							
North America	5 (26.3)	3 (13.0)	7 (30.4)	10 (43.5)	7 (35.0)	4 (18.2)	36 (27.7)
Western Europe	8 (42.1)	7 (30.4)	5 (21.7)	6 (26.1)	3 (15.0)	7 (31.8)	36 (27.7)
Eastern Europe	6 (31.6)	13 (56.5)	11 (47.8)	7 (30.4)	10 (50.0)	11 (50.0)	58 (44.6)

Fig 1 Study schematic.

Table 2 Analysis of complete response rate (intent-to-treat population). No differences in complete response between the vestipitant and ondansetron groups were observed based on posterior probability of success. NA, not applicable

	Ondansetron	Vestipitant					
	4 mg (*n*=19)	6 mg (*n*=24)	12 mg (*n*=23)	18 mg (*n*=22)	24 mg (*n*=20)	36 mg (*n*=22)	Total (*n*=111)
Complete response (*n*)	8	15	12	9	13	13	62
Complete response rate (%)	42.1	62.5	52.2	40.9	65.0	59.1	55.9
Improvement from control (vestipitant–ondansetron) %		20.4	10.1	−1.2	22.9	17.0	13.8
Posterior probability of success		0.222	0.052	0.039	0.065	0.254	N/A
Treatment failure (TF) [*n* (%)]	11 (57.9)	9 (37.5)	11(47.8)	13 (59.1)	7 (35.0)	9 (40.9)	49 (44.1)
Primary reason for TF [*n* (%)]							
Emesis/retching	7 (36.8)	3 (12.5)	1 (4.3)	3 (13.6)	1 (5.0)	2 (9.1)	10 (9.0)
Rescue medication	4 (21.1)	6 (25.0)	10 (43.5)	10 (45.5)	6 (30.0)	7 (31.8)	39 (35.1)
Emesis/retching after rescue medication (*n*)	1	1	6	2	2	4	15

response rate of 41% and the lowest posterior probability of success at 0.039, well below the cut-off of 0.457 (Table 2). The complete response rates with all other doses of vestipitant ranged from 52% to 65%. The vestipitant 6 and 24 mg groups both demonstrated a >20% improvement from ondansetron. A pairwise statistical analysis was neither planned nor performed. At interim analysis, applying the model-based approach, no dose along the response curve reached a posterior probability of success >0.900 applying the model-based approach. The model based approach had a cut-off posterior

probability >0.457 for the ≥20% complete response improvement over ondansetron objective. The highest posterior probability of success occurred near the 36 mg dose (posterior probability 0.254) but achieved neither the primary objective cut-off (>0.457) nor the futility hurdle (>0.300).

In all the vestipitant treatment groups, the reasons for treatment failure were primarily due to the requirement for further rescue medication (35%), rather than being due to emesis and retching (9%). In contrast, the reasons for treatment failure in the ondansetron arm were predominantly due to emesis and

retching (37%) compared with the need for further rescue medication (21%). Similar results were obtained when data excluded six patients with major protocol deviations.

The mean and median NNRS scores were similar in the vestipitant and ondansetron treatment groups with no difference between the patients with complete response or those with treatment failure (Supplementary Table S1). A mean decrease from baseline in the NNRS was observed; however, there was no apparent trend or pattern. In addition, the median time-to-PONV or discharge readiness for any vestipitant group was not statistically significantly different from the ondansetron group.

Safety

The proportion of subjects experiencing AEs were similar in all vestipitant treatment groups and the ondansetron group (Supplementary Table S2). As expected in this post-surgical population, procedural pain was the most frequently reported AE across all treatment groups. The frequency of reported AEs related to administration site was generally low across treatment groups (Supplementary Table S3). There were 12 AEs in seven patients (5.3%) that were considered related to vestipitant treatment; the AEs were most frequently observed in the vestipitant 18 mg group (five AEs in three patients, 13.0%) and the vestipitant 24 mg group (four AEs in two patients, 10.0%). There were seven SAEs reported in five patients (3.8%), in the vestipitant 6, 18, and 36 mg groups, all unrelated to vestipitant. The SAEs were most frequently reported in the vestipitant 18 mg group (four SAEs in two patients, 8.7%). In the ondansetron group, there were no related AEs and no SAEs. There were no AEs leading to withdrawal and no deaths reported in any treatment group in this study.

There were no clinically significant changes in clinical laboratory values (chemistry, haematology, and urinalysis), vital signs, or ECGs during this study.

Pharmacokinetics

Plasma PK parameters are summarized in Table 3. Plasma vestipitant C_{max} was highly variable after the rapid i.v. infusion. Plasma exposure to vestipitant appeared to increase in proportion to dose (95% confidence intervals of slope estimates from power models included 1.00 for C_{max} and AUC).

Discussion

In this study, the postoperative administration of vestipitant was no different from ondansetron 4 mg i.v. in surgical patients with PONV after failed ondansetron prophylaxis. This was observed at all doses of i.v. vestipitant, ranging from 6 to 36 mg. The primary endpoint for efficacy was the rate of patients exhibiting complete response, defined as no emesis and no further rescue medication from 10 min post-infusion up to 24 h or hospital discharge. The complete response rate for all doses of vestipitant combined was 56% compared with ondansetron at 42%. However, vestipitant was superior to ondansetron in decreasing the episodes of postoperative emesis and retching.

It should be noted that the patient population for this trial was predominantly women. However, this limitation is a logical consequence to the eligibility based on the Apfel risk score[15] reflecting the population most at risk for PONV. However, there is no convincing evidence that the response in men would be different with respect to antiemetic response. The difference in response would most likely be due to the differences in the control event rate in prevention studies.

The NNRS scores and the times to PONV or discharge were similar between the vestipitant and ondansetron treatment groups. In addition, administration of vestipitant and ondansetron in these surgical patients was safe and well tolerated with a low number of adverse events.

Although several strategies are available for the prevention of PONV, there are fewer effective treatment options after the onset of PONV.[16][17] This is primarily because of the difficulty of conducting interventional trials for PONV. Owing to the difficulty in predicting PONV after failed prophylaxis, these studies require screening a large number of patients, of which a small proportion may subsequently experience PONV and become eligible for enrolment into an interventional trial.[16][17] Furthermore, the pharmacodynamic features of the available preventive agents are different and some (such as

Table 3 Summary of PK parameters after single-dose i.v. infusion of vestipitant. Values are expressed as geometric mean [% coefficient of variation, (*n*)] or median [range, (*n*)]. AUC, area under the plasma drug concentration–time curve from 0 to time *t*, or extrapolated to time infinity; CL, total body clearance; C_{max}, maximum observed plasma concentration; t_{max} time to maximum observed plasma concentration; $t_{1/2}$, apparent terminal elimination half-life; V_{ss}, volume of distribution; *n*, number of randomized patients; [*n*], number of patients evaluable for PK parameter

Parameter	Vestipitant 6 mg (*n*=24)	Vestipitant 12 mg (*n*=23)	Vestipitant 18 mg (*n*=22)	Vestipitant 24 mg (*n*=20)	Vestipitant 36 mg (*n*=22)
AUC_{0-6} (ng h ml^{-1})	188 (71.0) [15]	219 (40.2) [14]	361 (37.6) [11]	495 (115.5) [12]	824 (37.3) [18]
AUC_{0-24} (ng h ml^{-1})	291 (47.4) [14]	433 (27.0) [12]	773 (34.8) [10]	1106 (45.3) [11]	1626 (35.3) [15]
AUC_{∞} (ng h ml^{-1})	308 (38.1) [11]	515 (27.5) [8]	789 (47.7) [5]	1221 (32.5) [5]	1354 (55.1) [4]
C_{max} (ng ml^{-1})	205 (305.7) [16]	204 (174.4) [17]	331 (150.8) [17]	423 (211.3) [16]	809 (123.5) [18]
t_{max} (h)	0.05 (0.03–0.08) [16]	0.05 (0.03–0.27) [17]	0.067 (0.03–1.00) [17]	0.05 (0.03–6.00) [16]	0.05 (0.03–0.27) [18]
$t_{1/2}$ (h)	7.71 (20.2) [11]	7.72 (20.5) [8]	9.69 (5.5) [5]	5.76 (40.2) [5]	6.79 (27.3) [4]
CL (litre h^{-1})	19.5 (38.1) [11]	23.3 (27.5) [8]	22.8 (47.7) [5]	19.6 (32.5) [5]	26.6 (55.1) [4]
V_{ss} (litre)	172 (93.3) [13]	261 (33.0) [11]	274 (28.0) [8]	189 (81.6) [9]	248 (39.8) [13]

dexamethasone) are not useful for the treatment of PONV because of low exposure and efficacy. In addition, for commercially funded trials, considerations regarding market share may also prevail. As a consequence, there are only a limited number of drugs, with different targets of action, which are available and licensed for the treatment of PONV. This number further decreases when considering the treatment of PONV, specifically in the setting of failed prophylaxis.

For these reasons, there are few systematic studies evaluating antiemetics for treatment of PONV after failed prophylaxis. In one prospective study, ondansetron was given as PONV prophylaxis and subjects that failed this prophylaxis were then randomized to receive a subsequent dose of ondansetron or placebo.[9] The study results indicate that ondansetron as a rescue for failed ondansetron PONV prophylaxis was no better than placebo (complete response placebo 32%, ondansetron 28%, *n*=214 each).[9] Despite publication of these data, ondansetron is frequently used as rescue treatment for PONV when prophylaxis with ondansetron has failed.

Habib and colleagues[7] performed a retrospective study of patients requiring rescue treatment after PONV prophylaxis from 2001 to 2005. Of 3062 patients who received ondansetron as both prophylaxis and rescue treatment for failed prophylaxis, only 50% were successfully rescued.[7] However, no placebo control was available in this retrospective study to put either the ondansetron or the promethazine rescue response rate in context with the Kovac and colleagues'[9] prospective study. A pilot study was completed evaluating ondansetron *vs* granisetron as rescue treatment after failed prophylaxis with ondansetron.[10] A total of 57% (*n*=30) had complete response after being given ondansetron rescue therapy, compared with 60% (*n*=30) and 68% (*n*=28) of those receiving 1 or 0.1 mg granisetron, respectively.[10] These three studies provided the basis for the informed prior for the efficacy of ondansetron in our model-based statistical approach (50% complete response). Our measured data were very consistent with our informed prior (ondansetron 42% complete response). Similarly, the ondansetron prophylaxis failure rate in our population (~25%) was consistent with the prophylaxis failure rate in both the studies by Kovac and colleagues[9] (19.5%) and Candiotti and colleagues (35%).[10]

In the current study, it is not known whether the PONV rescue rate with ondansetron was any better than placebo, since for ethical reasons, no placebo was tested. In the study by Kovac and colleagues,[9] the overall PONV rescue rate with ondansetron was 28% compared with the placebo rate of 32% in patients demonstrating inadequate ondansetron PONV prophylaxis. In addition to our study, two other studies have shown higher response rates with ondansetron, although no placebo was used. In a study by Diemunsch and colleagues[18] that compared ondansetron with metoclopramide for established PONV, treatment with ondansetron 4 mg i.v. was associated with a complete response in 44–59% of patients for vomiting and nausea, respectively. Similarly, in another study in patients with PONV after failure of prophylaxis with ondansetron, repeat doses of ondansetron 4 mg showed a complete response rate of 57%.[10] Despite the observations in

the study by Kovac and colleagues, there is good reason to assume that ondansetron in the study by Diemunsch and colleagues,[18] Candiotti and colleagues,[10] and in the current study had some effect and could have been better than placebo had placebo been tested.[4]

In this study, however, due to the predetermined goal to demonstrate 20% superiority in the overall complete response rate of vestipitant compared with ondansetron, further evaluation of vestipitant for the management of PONV was discontinued. Nonetheless, we conclude that these data support the hypothesis that vestipitant, at the doses tested, is effective in treating PONV. Further data are required to confirm these findings.

Supplementary material

Supplementary material is available at *British Journal of Anaesthesia* online.

Authors' contributions

P.K., J.T., P.D., L.E., and E.N.: were study investigators, provided feedback into the trial feasibility (all investigators) and strategy (P.K. and J.T.), participated in subject recruitment, clinical conduct, involved with review of the data analyses and contributions to the manuscript, and final approval. R.B.: participated in study design, data interpretation, served as the sponsor medical monitor, and involved with review and contributions to the manuscript, and final approval. B.J.: developed the pharmacokinetic analysis plan, data interpretation, involved with review and contributions to the manuscript, and final approval. S.R.: participated in study design, study management, reviewing the manuscript, and final approval. R.N.: participated in study design, data interpretation, revising the manuscript, and final approval.

Declaration of interest

All listed authors meet the criteria for authorship set forth by the International Committee for Medical Journal Editors. R.B., B.J., S.R., and R.N. are employees of GlaxoSmithKline (GSK). L.E. has been a paid lecturer for Grunenthal GmbH, Prostrakan GmbH, Fresenius GmbH. P.K. is an editor with the *European Journal of Anaesthesiology*. J.T. is an editor and on the editorial board of *British Journal of Anaesthesia*.

References

1 Gupta A, Wu CL, Elkassabany N, *et al.* Does the routine prophylactic use of antiemetics affect the influence of postdischarge nausea

and vomiting following ambulatory surgery? *Anesthesiology* 2003; **99**: 488–95

2 Habib AS, Gan TJ. Pharmacotherapy of postoperative nausea and vomiting. *Expert Opin Pharmacother* 2003; **4**: 457–73

3 Lehmann M, Monte K, Barach P, Kindler CH. Postoperative patient complaints: a prospective interview study of 12,276 patients. *J Clin Anesth* 2010; **22**: 13–21

4 Eberhart LH, Frank S, Lange H, *et al.* Systematic review on the recurrence of postoperative nausea and vomiting after a first episode in the recovery room: implications for the treatment of PONV and related clinical trials. *BMC Anesthesiol* 2006; **6**: 14

5 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

6 Kazemi-Kjellberg F, Henzi I. Treatment of established postoperative nausea and vomiting: a quantitative systematic review. *BMC Anesthesiol* 2001; **1**: 2

7 Habib AS, Reuveni J, Taguchi A, *et al.* 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

8 George E, Hornuss C, Apfel CC. Neurokinin-1 and novel serotonin antagonists for postoperative and postdischarge nausea and vomiting. *Curr Opin Anaesthesiol* 2010; **23**: 714–21

9 Kovac AL, O'Connor TA, Pearman MH, *et al.* Efficacy of repeat intravenous dosing of ondansetron in controlling postoperative nausea and vomiting: a randomized, double-blind, placebo-controlled multicenter trial. *J Clin Anesth* 1999; **11**: 453–9

10 Candiotti KA, Nhuch F, Kamat A, *et al.* Granisetron versus ondansetron treatment for breakthrough postoperative nausea and vomiting after prophylactic ondansetron failure: a pilot study. *Anesth Analg* 2007; **104**: 1370–3

11 ZOFRAN® (ondansetron hydrochloride) injection for intravenous use. Prescribing Information. Research Triangle Park, NC: GlaxoSmithKline, 2013

12 Brigandi RA, Russ SF, Petit C, *et al.* Intravenous pharmacokinetics, local tolerability, and hemolysis of an SBE7-β-cyclodextrin formulation of the Neurokinin-1 receptor antagonist vestipitant. *Clin Pharm Drug Dev* 2014, doi: 10.1002/cpdd.128

13 Kacina K, Noble R, Chen P, Brigandi R. Bayesian adaptive phase ii trial combining proof of concept and dose-finding: comparison of potential models. *Joint Statistical Meetings*. San Diego, CA: July 31, 2012; 2081909

14 Chow SC, Liu JP. *Design and Analysis of Bioavailability and Bioequivalence Studies*, 3rd Edn. Boca Raton, FL: Chapman & Hall/CRC, 2009

15 Apfel CC, Heidrich FM, Jukar-Rao S, *et al.* Evidence-based analysis of risk factors for postoperative nausea and vomiting. *Br J Anaesth* 2012; **109**: 742–53

16 Kranke P, Eberhart LHJ. Possibilities and limitations in the pharmacological management of postoperative nausea and vomiting. *Eur J Anaesthesiol* 2011; **28**: 758–65

17 Jokinen J, Smith AF, Foewer N, Eberhart LH, Kranke P. Management of postoperative nausea and vomiting: how to deal with refractory PONV. *Anesthesiol Clin* 2012; **30**: 481–93

18 Diemunsch P, Conseiller C, Clyti N, Mamet JP, Ondansetron compared with metoclopramide in the treatment of established postoperative nausea and vomiting. The French Ondansetron Study Group. *Br J Anaesth* 1997; **79**: 322–6

Handling editor: M. M. R. F. Struys