British Journal of Anaesthesia **99 (2):** 202–11 (2007)
doi:10.1093/bja/aem133 Advance Access publication May 30, 2007

BJA

Single-dose aprepitant *vs* ondansetron for the prevention of postoperative nausea and vomiting: a randomized, double-blind Phase III trial in patients undergoing open abdominal surgery†

P. Diemunsch[1]*, T. J. Gan[2], B. K. Philip[3], M. J. Girao[4], L. Eberhart[5], M. G. Irwin[6], J. Pueyo[7], J. E. Chelly[8], A. D. Carides[9], T. Reiss[9], J. K. Evans[9] and F. C. Lawson[9] for the Aprepitant-PONV Protocol 091 International Study Group‡

[1]Services d'Anesthesiologie-Reanimation Chirurgicale, CHU, Hôpital de Hautepierre, 1 Avenue de Moliere, Strasbourg 67000, France. [2]Department of Anesthesiology, Duke University Medical Centre, Durham, NC 27710, USA. [3]Department of Anesthesiology, Perioperative and Pain Medicine, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115, USA. [4]Universidade Federal de Sao Paulo, Rua Napoleao de Barros, 715-7 o ander, Sao Paulo, Brazil. [5]University of Marburg, Abteilung Anaesthesie und Intensivetherapie, Baldingerstr. 1, Marburg, Germany. [6]Department of Anaesthesiology, University of Hong Kong, 102 Pokfulam Road, Pokfulam, Hong Kong, Republic of China. [7]Clinica Universitaria de Navarra, Avda. Pio XII, 36, Pamplona, Navarra 31008, Spain. [8]Department of Anesthesiology, University of Pittsburgh Medical Center, 5230 Centre Avenue, M-140, Pittsburgh, PA 15232, USA. [9]Merck Research Laboratories, West Point, PA 19486, USA

**Corresponding author: Services d'Anesthesiologie-Reanimation Chirurgicale, CHU, Hôpitale de Hautepierre, 1 Avenue de Moliere, Strasbourg 67000, France. E-mail: pierre.diemunsch@chru-strasbourg.fr*

Background. The neurokinin$_1$ antagonist aprepitant is effective for prevention of chemotherapy-induced nausea and vomiting. We compared aprepitant with ondansetron for prevention of post-operative nausea and vomiting.

Methods. Nine hundred and twenty-two patients receiving general anaesthesia for major abdominal surgery were assigned to receive a single preoperative dose of oral aprepitant 40 mg, oral aprepitant 125 mg, or i.v. ondansetron 4 mg in a randomized, double-blind trial. Vomiting episodes, use of rescue therapy, and nausea severity (verbal rating scale) were documented for 48 h after surgery. Primary efficacy endpoints were complete response (no vomiting and no use of rescue therapy) 0–24 h after surgery and no vomiting 0–24 h after surgery. The secondary endpoint was no vomiting 0–48 h after surgery.

Results. Aprepitant at both doses was non-inferior to ondansetron for complete response 0–24 h after surgery (64% for aprepitant 40 mg, 63% for aprepitant 125 mg, and 55% for ondansetron, lower bound of 1-sided 95% CI$>$0.65), superior to ondansetron for no vomiting 0–24 h after surgery (84% for aprepitant 40 mg, 86% for aprepitant 125 mg, and 71% for ondansetron; $P<0.001$), and superior for no vomiting 0–48 h after surgery (82% for aprepitant, 40 mg, 85% for aprepitant, 125 mg, and 66% for ondansetron; $P<0.001$). The distribution of peak nausea scores was lower in both aprepitant groups *vs* ondansetron ($P<0.05$).

Conclusions. Aprepitant was non-inferior to ondansetron in achieving complete response for 24 h after surgery. Aprepitant was significantly more effective than ondansetron for preventing vomiting at 24 and 48 h after surgery, and in reducing nausea severity in the first 48 h after surgery. Aprepitant was generally well tolerated.

Br J Anaesth 2007; **99**: 202–11

Keywords: aprepitant; clinical trials; PONV; ondansetron; serotonin (5-hydroxy-tryptamine), antagonism

Accepted for publication: April 11, 2007

†*Declaration of interest*. This study was funded by Merck and Co., Inc. (Sponsor), West Point, PA 19486, USA. Drs Diemunsch, Gan, Philip, Girao, Eberhart, Irwin, Pueyo and Chelly received funding from Merck to perform the study. Drs Carides, Reiss, Evans and Lawson are employees of Merck and hold stock options or stock in Merck.
‡Participating primary investigators are listed in Acknowledgements.

Nausea and vomiting occur in as many as 70–80% of patients in the first 24 h after surgery.[1–5] Even among patients who receive antiemetic prophylaxis with i.v. $5HT_3$ receptor antagonists (RAs) or other drugs, 30–40% still experience postoperative nausea and vomiting (PONV).[6] Thus, an unmet medical need for improved PONV prophylaxis exists. A new class of drug known as non-peptide neurokinin$_1$ (NK_1) RAs has demonstrated activity against both peripheral and central emetic stimuli in animal models.[7–9] Consistent with the idea that antagonism at the NK_1 receptor could affect the response to emetic stimuli,[10–13] evidence suggesting the potential efficacy of NK_1 RAs against PONV was obtained in clinical trials of two different drugs in this class, which were assessed in patients undergoing major gynaecological surgery.[14] In one study, a significantly lower incidence of vomiting in the first 24 h after surgery was observed with an NK_1 RA given either alone or in combination with a $5HT_3$ RA, compared with the $5HT_3$ RA alone.[15] In another study, an NK_1 RA given to patients with established PONV was superior to placebo in controlling vomiting.[16]

Aprepitant, a highly selective, brain-penetrant NK_1 RA with a long half-life and preclinical efficacy against opioid-induced emesis,[7 9 17] has demonstrated efficacy against chemotherapy-induced nausea and vomiting when combined with other antiemetics, and is the first in its class to be approved for this indication.[17] To examine the possibility that it may also provide benefit against PONV, an initial Phase IIb/III study of aprepitant *vs* the $5HT_3$ RA ondansetron was conducted in patients undergoing open abdominal surgery.[18] In that study, which was the first trial of aprepitant for prevention of PONV, the treatments showed similar efficacy for the primary endpoint of complete response (no vomiting and no use of rescue), but aprepitant provided greater protection against vomiting during the first 24 and 48 h after surgery. The present study was conducted to confirm these positive results in an international population, more thoroughly assess the clinical profile of aprepitant by comparing it with ondansetron for no vomiting and other endpoints, and to define better the apparent similarity for complete response seen in the first study comparing aprepitant and ondansetron.

Methods

A total of 42 centres (eight U.S. sites and 34 non-U.S. sites in North America, South America, Europe, Australia, and Asia) participated in this randomized double-blind study (Protocol 091) between May 28, 2004 and April 20, 2005. Approval from the Institutional Review Board for each centre was obtained and all patients gave written informed consent.

Patients

Patients, aged ≥18 yr old, ASA I–III, undergoing open abdominal surgery requiring at least one overnight hospital stay and receiving volatile-agent-based general anaesthesia including nitrous oxide were enrolled. Among exclusion criteria were pregnancy/breastfeeding status, need for a nasogastric or oral-gastric tube, use of neuroaxial- or propofol-maintained anaesthesia, vomiting within 24 h before surgery or of any organic aetiology, allergy to any medications to be used before operation or intra-operatively, pre-established need for intensive care or step-down unit care after operation, evidence of disease or history of illness which according to the investigator rendered the patient inappropriate for the study, abnormal preoperative laboratory values (aspartate aminotransferase >2.5×upper limit of normal, alanine aminotransferase >2.5×upper limit of normal, bilirubin >1.5×upper limit of normal, or creatinine >1.5×upper limit of normal), or need for opioid antagonists or benzodiazepine antagonists. Medications known to induce CYP3A4, such as phenytoin, carbamazepine, barbiturates, rifampicin, or rifabutin, were prohibited within 30 days of the study start; those known to be CYP3A4 substrates (terfenadine, pimozide, cisapride, or astemizole) or CYP3A4 inhibitors (clarithromycin, ketoconazole, or itraconazole) were prohibited within 7 days of the study start.

The gender-stratified randomization schedule was computer-generated by the sponsor. In order to ensure in-house blinding, the schedule was created by an assistant statistician who was otherwise not involved with the study. On the day of surgery, patients were randomized to receive one of three antiemetic treatments before operation: oral aprepitant 40 mg, oral aprepitant 125 mg, or i.v. ondansetron 4 mg. Patient and investigator blinding was maintained with matching placebos. The sponsor provided supplies of aprepitant, placebo matching aprepitant, and blinded allocation schedules. Each site designated an unblinded pharmacist otherwise not involved with the study to receive, store, and prepare the ondansetron and saline placebo.

Aprepitant or placebo was given within 3 h of anticipated induction of anaesthesia, and i.v. ondansetron or placebo was infused over 2–5 min immediately before induction, as indicated in the approved prescribing information for ondansetron.[19]

The anaesthesia regimen consisted of optional premedication with a benzodiazepine; induction with any anaesthetic agent; neuromuscular blocking agents; opioids; maintenance of anaesthesia with nitrous oxide (50–70%) with a volatile anaesthetic; and neostigmine (2–5 mg) as needed. Additional prophylactic antiemetics were prohibited within 24 h before or after surgery except for postoperative rescue therapy, which was offered if the patient requested it, had nausea lasting longer than 15 min, or had >1 episode of vomiting/retching. The type of rescue therapy was chosen by the investigator.