Ondansetron has similar clinical efficacy against both nausea and vomiting

R. M. Jokela,1 O. S. Cakmakkaya,2,3 O. Danzeisen,4 K. T. Korttila,5 P. Kranke,6 A. Malhotra,7 A. Paura,8 O. C. Radke,9 D. I. Sessler,10 A. Soikkeli,11 N. Roewer12 and C. C. Apfel13

1 Staff Anaesthesiologist, 11 Staff Anaesthesiologist, Helsinki University Hospital, Helsinki, Finland
2 Staff Anaesthesiologist, Cerrahpasa Medical School, University of Istanbul, Istanbul, Turkey
3 Visiting Research Associate, 7 Clinical Research Fellow, 9 Visiting Associate Professor, 13 Associate Professor, Perioperative Clinical Research Core, Department of Anesthesia and Perioperative Care, University of California at San Francisco, CA, USA
4 Staff Anaesthesiologist, University of Freiburg, Freiburg, Germany
5 Professor and Chair, Department of Anaesthesiology, Helsinki University, Helsinki, Finland
6 Staff Anaesthesiologist, 12 Professor and Chair, Department of Anaesthesiology, University of Würzburg, Germany
8 Staff Anaesthesiologist, Klinikum Lüneburg, Lüneburg, Germany
10 Professor and Chair, Department of Outcomes Research, The Cleveland Clinic, Cleveland, OH, USA

Summary

Ondansetron is widely believed to prevent postoperative vomiting more effectively than nausea. We analysed data from 5161 patients undergoing general anaesthesia who were randomly stratified to receive a combination of six interventions, one of which was 4 mg ondansetron vs placebo. For the purpose of this study a 20% difference in the relative risks for the two outcomes was considered clinically relevant. Nausea was reduced from 38% (969/2585) in the control to 28% (715/2576) in the ondansetron group, corresponding to a relative risk of 0.74, or a relative risk reduction of 26%. Vomiting was reduced from 17% (441/2585) to 11% (293/2576), corresponding to a relative risk of 0.67, or a relative risk reduction of 33%. The relative risks of 0.67 and 0.74 were clinically similar and the difference between them did not reach statistical significance. We thus conclude that ondansetron prevents postoperative nausea and postoperative vomiting equally well.

Correspondence to: Christian C. Apfel
E-mail: apfelc@anesthesia.ucsf.edu or apfel@ponv.org
Accepted: 18 August 2008

Despite considerable effort and countless trials evaluating antiemetic strategies, the overall incidence of postoperative nausea and vomiting (PONV) remains around 25–30% [1–4]. The term PONV is used in reports to include both nausea and vomiting; however, the two responses are different biological phenomena and should be reported and analysed separately [5, 6]. Furthermore, a recent epidemiologic study by Stadler et al. [7] found that while most risk factors are predictive for both outcomes, some appear to be predictive for nausea only. It is thus conceivable that a drug used for the prevention of PONV may be more effective for one outcome than for the other.

Consistent with this theory, the authors of a systematic review concluded that ondansetron prevents vomiting better than nausea [8], a conclusion that has since been widely accepted [4]. However, the conclusion of this systemic review is tempered by the fact that few studies separately report all relevant outcomes. Consequently, relative efficacies for nausea and vomiting were determined across all studies rather than strictly from studies that adequately evaluated both responses.

We have previously designed [9] and reported [10] on an International Multicenter Protocol to assess the single and combined benefits of Antiemetic strategies in a Controlled clinical Trial of factorial design (IMPACT) that investigated the effect of six interventions on PONV. The results of IMPACT allow us to directly, and with high power, investigate whether ondansetron comparably reduces the relative risks for nausea and for vomiting or...
if there is a clinically relevant difference. Of note, a clinically relevant difference is defined distinctly from a statistically significant difference. For example, an absolute difference in relative risks for nausea and vomiting of 0.01 could reach statistical significance but would be highly unlikely to have any clinical meaning, i.e., the effect on each outcome is actually quite similar. For the purposes of this analysis, a minimal clinically important difference (MCID) was defined as an absolute difference in relative risks of > 0.2 [11].

Methods

Protocol

The details of the protocol are described elsewhere [9, 10]. In brief, adult patients scheduled for surgery under general anaesthesia met eligibility criteria if they had at least two predictors of the simplified risk score for PONV, i.e., their calculated risk for PONV exceeded 40% [12]. The considered risk factors were: female gender, previous history of PONV and/or motion sickness, non-smoking status, and the anticipated use of postoperative opioids.

With ethics committee approval and informed consent, participating patients were randomised to receive a combination of the six study interventions: 4 mg ondansetron vs placebo, 4 mg dexamethasone vs placebo, 1.25 mg droperidol vs placebo, propofol vs volatile anaesthetic, air vs nitrous oxide, and remifentanil vs fentanyl. The timing of ondansetron administration was based on the trials of Sun et al. [13] and Tang et al. [14], in which administering ondansetron near the end of surgery appeared to be more effective for the prevention of PONV.

Patients were monitored for nausea and vomiting for the first 24 h after surgery. The time, severity, and characteristics of any emetic episode were recorded on standardised forms. Any emetic episodes (either retching or vomiting) were considered as postoperative vomiting. Patients who experienced postoperative nausea (PON), postoperative vomiting (POV), or both were considered having suffered postoperative nausea and vomiting (PONV) [6]. Rescue anti-emetic medication was provided as described previously [9, 10].

At 2 and 24 h after surgery, an investigator blinded to treatment recorded emetic episodes and the patient’s self-assessment of their strongest nausea during the preceding time interval using an 11-point verbal rating scale [6].

Statistical analysis

The primary outcomes for these analyses were the incidences of nausea (PON), vomiting (POV), and postoperative nausea and vomiting (PONV) for 24 h after anaesthesia. The data which we analysed were from a study that tested six interventions; however, this report focuses solely on the effect of ondansetron on PONV. The remaining five factors were balanced within the two arms (i.e., ondansetron and placebo) due to the factorial design, and are thus unlikely to have confounded the results [9, 10].

Since nausea and vomiting were reported concurrently in the same patients, the outcomes are best described as correlated responses. Currently, there is no adequate statistical test available for comparison of correlated responses to a single intervention. Instead, relative risks were calculated for each outcome and compared to assess for a clinically significant difference, defined conservatively as a difference in relative risks > 0.2.

Results

Informed consent was obtained from 5262 patients. Sixty-three patients withdrew from the study before allocation, leaving 5199 patients who were randomised to ondansetron or placebo. Thirty-eight additional patients were excluded for incomplete outcome records. Consequently, we included 5161 patients randomised to ondansetron or placebo in our analysis.

Table 1 Risk factors and calculated risk for PONV. Results presented as number of patients (%) or as mean (SD), as indicated.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Control (n = 2585)</th>
<th>Ondansetron (n = 2576)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female gender</td>
<td>2096 (81)</td>
<td>2110 (82)</td>
<td>0.427</td>
</tr>
<tr>
<td>Age; years</td>
<td>47 (15)</td>
<td>47 (15)</td>
<td>0.238</td>
</tr>
<tr>
<td>Non-smoking status</td>
<td>2109 (82)</td>
<td>2082 (81)</td>
<td>0.483</td>
</tr>
<tr>
<td>History of PONV</td>
<td>863 (33)</td>
<td>859 (35)</td>
<td>0.251</td>
</tr>
<tr>
<td>History of motion sickness</td>
<td>862 (33)</td>
<td>875 (34)</td>
<td>0.637</td>
</tr>
<tr>
<td>Duration of anaesthesia; min</td>
<td>109 (65)</td>
<td>111 (64)</td>
<td>0.225</td>
</tr>
<tr>
<td>Type of surgery (abdominal)</td>
<td>1138 (44.2)</td>
<td>1158 (44.8)</td>
<td>0.676</td>
</tr>
<tr>
<td>Postoperative opioids</td>
<td>2002 (78)</td>
<td>2029 (80)</td>
<td>0.276</td>
</tr>
<tr>
<td>Risk score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0*</td>
<td>2 (0)</td>
<td>6 (0)</td>
<td>0.434</td>
</tr>
<tr>
<td>1*</td>
<td>118 (5)</td>
<td>104 (4)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>628 (25)</td>
<td>621 (24)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1068 (42)</td>
<td>1047 (41)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>739 (29)</td>
<td>771 (30)</td>
<td></td>
</tr>
<tr>
<td>Calculated risk for PONV</td>
<td>0.59 (0.17)</td>
<td>0.59 (0.17)</td>
<td>0.373</td>
</tr>
</tbody>
</table>

*Patients with 0–1 risk factors were anticipated to have 2+ risk factors prior to randomisation but later did not (e.g., no need for postoperative opioids).
5161 patients, 826 (16.0%) had at least one episode of PONV within 2 h after surgery, 1437 (27.8%) had at least one episode between 2 and 24 h after surgery, and 1731 (33.5%) had an episode within 24 h of surgery.

During the first 2 h after surgery, ondansetron prevented nausea and vomiting similarly, with a RR of 0.68 (0.59, 0.77) for nausea and 0.63 (0.48, 0.82) for vomiting (Table 2). During the interval of 2–24 h after surgery, the RR was 0.75 (0.68, 0.82) for nausea and 0.69 (0.59, 0.81) for vomiting. For the entire study period (0–24 h), ondansetron had RRs of 0.74 (0.68, 0.80) and 0.67 (0.58, 0.77) for nausea and vomiting, respectively (Fig. 1).

Discussion

In this large, randomised, controlled, multicentre trial, the RR for nausea was 0.74 (0.68, 0.80) and for vomiting was 0.67 (0.58, 0.77), a difference that is highly unlikely to be clinically relevant. In addition, the overlapping of the 95% confidence intervals suggests that the effect of ondansetron on the two outcomes is not significantly different. In any study in which the null hypothesis is accepted, it is important to confirm that there is sufficient power to detect a meaningful difference, i.e. to distinguish between a lack of evidence and evidence for a lack of effect. This trial included over 5000 subjects randomised to receive ondansetron or placebo. An issue with a study this size is quite the opposite; it is powered to detect even small differences that may become statistically significant, even if no longer clinically meaningful. Our point estimates indicate that the difference in the two outcomes is 0.07, which, even if statistically significant, would not be clinically relevant. Thus, it is fair to conclude that ondansetron reduces the relative risks for both post-operative nausea and vomiting to a similar degree clinically.

This result contrasts with the generally held opinion that ondansetron has greater anti-vomiting than anti-nausea effect [4]. A review of the literature reveals that this assumption was based on a meta-analysis that concluded ‘the anti-nausea effect is less pronounced’ [8]. A closer look at that study reveals that analysis for the anti-nausea effect excluded two studies because they reported the prevention of nausea by ondansetron to be twice that reported in other trials. While it is well-accepted practice to present results without outliers, those two studies were included in the anti-emetic analysis.
that ondansetron may actually have prevented needed-to-treat for vomiting of 6.4 (5.3–7.9), suggesting vent nausea of 4.6 (4.0–5.5) was smaller than the number-vomiting in that comparison were, in fact, very similar only 0.02, demonstrating that the RRs of nausea and of vomiting in the prevention group, which translates to a RR for vomiting of 0.64. The absolute difference in relative risks was thus corresponding overall incidences of vomiting were 43.7% (997⁄1908) in the control and 41.4% (789⁄1740) in the prevention group, which translates to a RR for nausea of 0.66. The number-needed-to-treat to prevent nausea of 4.6 (4.0–5.5) was smaller than the number-needed-to-treat for vomiting of 6.4 (5.3–7.9), suggesting that ondansetron may actually have prevented more nausea than vomiting (of course, this is due to the higher baseline incidence of nausea compared to vomiting and not a specific outcome efficacy of the drug).

We therefore conclude that ondansetron’s clinical effect is to comparably reduce the relative risks of postoperative nausea and postoperative vomiting. This finding is of particular relevance in the common clinical scenario of designing a multiple drug antiemetic regimen, as it is not necessary to consider the anti-nausea vs anti-vomiting efficacies of ondansetron separately.

Acknowledgements

This study was supported by the Department of Anesthesiology, University of Würzburg, Grant 1518 TG 72, Josef-Schneider Str. 2, D-97080 Würzburg, Germany; Helsinki University Hospital, HUS-EVO Grants TYH 0324, TKK 2120 and TKK 3120, University of Helsinki, Helsinki, Finland; Biomedicum Helsinki Foundation, Haartmaninkatu 8, FIN-00029 HUCH, Finland; Finnish Medical Foundation, Kalevankatu 11 A, FIN-00100 Helsinki, Finland; Maud Kuistila Foundation, Mannheimintie 12 B, FIN-00101 Helsinki, Finland; Paulo Foundation, Tiistinniityntie 4, FIN-02231 Espoo, Finland; and Research Foundation of Orion Corporation, Orionintie 1, FIN-02200 Espoo, Finland; NIH Grant GM 061655 (Bethesda, MD), the Gheens Foundation (Louisville, KY), the Joseph Drown Foundation (Los Angeles, CA), and the Commonwealth of Kentucky Research Challenge Trust Fund (Louisville, KY).

References


![Figure 2](image-url)
benefits of antiemetic interventions in a controlled clinical trial of a $2 \times 2 \times 2 \times 2 \times 2$ factorial design (IMPACT). Controlled Clinical Trials 2003; 24: 736–51.


