A Double-Blind Comparison of Intravenous Ondansetron and Placebo for Preventing Postoperative Emesis in 1- to 24-Month-Old Pediatric Patients After Surgery Under General Anesthesia

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We assessed the efficacy and safety of ondansetron (0.1 mg/kg IV) prophylactically administered before surgery for prevention of postoperative vomiting (POV) in a double-blind, placebo-controlled study of 670 pediatric patients, 1- to 24-mo-old, undergoing elective surgery under general anesthesia. The study enrolled 335 children in each treatment group (ondansetron versus placebo). Significantly fewer children treated with ondansetron exhibited emesis or discontinued the study prematurely after surgery (ondansetron, 11%; placebo, 28%; odds ratio = 0.33; P < 0.0001). The number required to treat prophylactically with ondansetron to prevent POV was approximately six. Ondansetron treatment also resulted in fewer patients requiring rescue medication or assumed to have had rescue upon early discontinuation from the study during the postoperative period (ondansetron, 5%; placebo, 10%) and less emesis (0 of 6) after rescue medication when compared with placebo (7 of 21). The incidence of POV and other antiemetic effects of ondansetron were similar in children aged 1–12 mo and 13–24 mo and in children prospectively expected or not expected to require opioids as part of their anesthetic or analgesic management. Ondansetron was well tolerated; the incidence of adverse events considered possibly related to study drug was similar between treatment groups (ondansetron, 1.8%; placebo, 1.5%).


Postoperative nausea and vomiting (PONV) is a common complication of surgery (1–4) and a leading complaint from parents of pediatric surgical patients (4). Severe vomiting is unpleasant and is a leading cause of delayed discharge and unplanned readmission after surgery (2,5,6). Pediatric patients overall are more likely to develop PONV than adults (7–9), with rates of more than 50% associated with strabismus surgery, tonsillectomy/adenoidectomy, orchidopexy, and hernia repair (3,10–12). Less frequent rates for postoperative vomiting (POV) have been reported for the youngest children: <10% in children up to 1 yr of age and approximately 20% in children 1–2 yr of age (13).

Ondansetron HCl, a selective serotonin receptor antagonist, is well tolerated and effective in preventing PONV in adults and children (14–18). However, less information is available on the use of ondansetron in patients younger than 2 yr old. This prospective, randomized, double-blind, placebo-controlled study was conducted to evaluate the efficacy and safety of ondansetron in the prevention
of postoperative emesis in pediatric surgical patients 1–24 mo of age.

Methods

After Ethics Committee/Review Board approval and parental/guardian informed consent, 670 patients from 28 investigative sites were randomized to double-blind prophylactic antiemetic treatment with ondansetron (335 patients) or placebo (335 patients). Inclusion criteria were: male or female, ASA physical status I, II, or III, 1 to 24 mo old, and elective inpatient or outpatient surgery under general anesthesia. Cardiac surgery, neurosurgery, halothane, and propofol administration were excluded, as were patients who experienced emesis during the 24 h before surgery or who received phenothiazine, metoclopramide, or systemic corticosteroids within 48 h of study drug administration.

After the induction of general anesthesia, but before surgery, patients received a single IV dose of ondansetron HCl (ZOFTRAN® Injection, 2 mg/mL), 0.1 mg/kg, or placebo (saline) over 30 s. Treatment assignment was stratified according to expected opioid usage during anesthesia or after surgery. The dose of ondansetron was based on a pharmacokinetic study of 1- to 24-mo-old patients1 and was consistent with previously published pediatric studies (16–18) and recently published consensus guidelines (4). A 1:1 randomization schedule was used. Study drug was prepared by an unblinded pharmacist at the investigative site.

A sample size of 600 patients was estimated to provide 80% power to test the null hypothesis (no difference in incidence of emesis between ondansetron and placebo in the intent-to-treat population) using a two-sided type I error probability of 5% and assuming a 15% dropout rate and an underlying emetic rate of 15% in the placebo group and 7.5% in the ondansetron group.

The primary efficacy end-point was the proportion of patients who experienced at least one emetic episode during a postoperative 24-h assessment period beginning with discontinuation of anesthesia. An emetic episode was defined as a single vomit or retch or any number of continuous vomits or retches separated by the absence of both vomiting and retching for at least 3 min. Secondary efficacy end-points included median time to first emetic episode, median time to first rescue medication, proportion of patients who received rescue medication, and proportion of patients who experienced emesis after receiving rescue medication. A rescue medication was defined as one that was given specifically for treatment of emesis during the 24-h assessment period and could include ondansetron. Rescue medication was administered at the discretion of the investigator, when medically indicated, when 3 emetic episodes occurred within a 15-min period, or at any time upon subject/parent/guardian request.

Patients prematurely withdrawn from the study without experiencing an emetic episode were assumed to have had an emetic episode, with the time of withdrawal recorded in place of time of emetic episode. If rescue medication was administered in the absence of emesis, the patient was considered to have had emesis, and the time of rescue was considered as the time of emetic episode. For patients with incomplete or missing data, time of last known contact was considered as the time of emetic episode. Where patients experienced emesis or received rescue medication before discontinuation of anesthesia but after the administration of study drug, the time of emesis or time of rescue, respectively, was set at zero. Subjects who completed the study without experiencing any emetic episodes and without requiring rescue medication(s) were censored at the end of the 24-h postoperative assessment period.

For the primary efficacy end-point, the null hypothesis was tested using the Cochran-Mantel-Haenszel (CMH) test, which tested for a difference between treatment groups in the proportion of patients with at least one emetic event while controlling for the effect of expected opioid use. The homogeneity of odds ratios across expected opioid/non-opioid strata was tested using the Breslow-Day statistic. A logistic regression model was used to examine the relationship between occurrence of emesis and potential prognostic factors, including age, sex, race, ASA classification, and anticipated opioid use, as well as treatment. Secondary event-time end-points were analyzed based on the Cox proportional-hazards regression model, with the same covariates as for the logistic regression. The primary safety assessment consisted of evaluation of adverse events (AE) gathered by consultation with parents or guardians or direct observation during the study and, in the case of outpatients, by telephone interviews with parents or guardians at the end of the 24-h assessment period. Because emesis (vomiting or retching) was recorded as part of the efficacy assessment, it was not considered an AE in this study. AE data were analyzed descriptively.

Results

Of the 670 patients, 323 (96%) ondansetron-treated and 321 (96%) placebo-treated patients completed the study, and 12 (4%) ondansetron-treated and 14 (4%)
placebo-treated patients were discontinued before completion of study assessments. The reasons for discontinuation were similar in both groups and included lost to follow-up, protocol violation, and AEs.

Demographic data and baseline characteristics were comparable for ondansetron- and placebo-treated patients (Table 1). The mean age, weight, and height were similar between treatment groups. Most patients in each group were male, white or black, ASA physical status I or II, and outpatients undergoing similar surgical procedures. Each group had similar proportions of patients with histories of previous POV after general anesthesia (~10%) and motion sickness (~1%). A total of 196 (59%) patients in the ondansetron group and 194 (58%) patients in the placebo group were expected to receive one or more opioids for anesthesia or after surgery during the study, but postrandomization events caused some changes in the predicted use of opioids. In actual use, more patients received opioids than expected (272 ondansetron-treated patients and 264 placebo-treated patients); however, the percentage of patients receiving opioids in each group was similar (81% and 79% in the ondansetron and placebo groups, respectively).

Prophylactic administration of ondansetron after the induction of general anesthesia and before the start of surgery resulted in a significantly smaller proportion of patients with postoperative emesis (11%) during the 24-h observation period after discontinuation of anesthesia than prophylactic administration of placebo (28%) (Table 2). The CMH test, adjusted for the effect of expected opioid strata, provided an odds ratio of 0.33 (P < 0.0001), which indicated that the odds of emesis after ondansetron were approximately one third of those after placebo. The number of patients required to treat prophylactically with ondansetron to prevent postoperative emesis in one patient was approximately six. Ondansetron-treated patients also exhibited a longer median time from discontinuation of anesthesia to the first emetic event than placebo-treated patients (207 min versus 135 min) (Table 2).

Figure 1 depicts cumulative survival curves for emesis for ondansetron- and placebo-treated patients in the expected opioid and non-opioid strata. These strata were not substantially different with regard to the proportion of patients exhibiting emesis and the times to first emetic event. Because of the unexpectedly large number of subjects who received opioids on trial, a post hoc reevaluation of efficacy results was performed based on actual opioid usage. Prophylactic administration of ondansetron continued to show an improvement in control of postoperative emesis in those subjects who actually received opioids as part of their operative or postoperative management (data not shown). The efficacy of ondansetron versus placebo was also not significantly affected by age, sex, race, or ASA physical status (data not shown). Analysis of the incidence of emesis for placebo- and ondansetron-treated patients by age category revealed comparable background (placebo) versus ondansetron incidences for 1- to 12-mo-old patients (27% versus 8%) and 13- to 24-mo-old patients (28% versus 15%). Overall, fewer ondansetron-treated patients (n = 18; 5%) received rescue medication(s) or were assumed to have had rescue upon early discontinuation from the study compared with placebo-treated patients (n = 32; 10%). The overall stratum-adjusted treatment comparison was significant at P = 0.025. A hazard ratio of 0.52 indicated a 48% reduction in the need for rescue with ondansetron compared with placebo. The median time to first rescue antiemetic or withdrawal was 85 min (n = 18) after ondansetron treatment and 91 min (n = 32) after placebo treatment (not shown). Rescue medications included dexamethasone, dimenhydrinate, dimethicone, dolasetron, metoclopramide, and ondansetron. The effect of ondansetron versus placebo on the need for rescue medication was not affected by expected opioid use, age, sex, race, or ASA physical status of the patients.

Of the 21 patients in the placebo group who actually received rescue medication, 7 experienced at least one emetic episode after medication administration. None of the six rescued patients in the ondansetron group experienced emesis after the administration of rescue medication.

Patients underwent a wide variety of surgical procedures. As shown in Table 3, ondansetron-treated patients exhibited less emesis than placebo-treated patients for each of the six most commonly performed surgeries. The mean ± SD duration of anesthesia was similar in the ondansetron (79.6 ± 53.6 min) and placebo (80.1 ± 54.3 min) groups.

**Table 1. Demographics and Baseline Characteristics**

<table>
<thead>
<tr>
<th>Demographic/characteristic</th>
<th>Placebo (n = 335)</th>
<th>Ondansetron (n = 335)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mo)a</td>
<td>12.2 ± 6.0</td>
<td>12.7 ± 6.3</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>9.8 ± 2.3</td>
<td>10.0 ± 2.4</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>73.9 ± 8.6</td>
<td>74.1 ± 10.3</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F, M (%)</td>
<td>25, 75</td>
<td>24, 76</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>white, black, all othersb</td>
<td>63, 16, 21</td>
<td>66, 13, 21</td>
</tr>
<tr>
<td>ASA physical status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I, II, III (%)</td>
<td>72, 27, 1</td>
<td>74, 25, &lt;1</td>
</tr>
<tr>
<td>Surgical status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>outpatient, inpatient (%)</td>
<td>86, 14</td>
<td>85, 15</td>
</tr>
</tbody>
</table>

a One patient in the ondansetron group was 42 mo of age.
b Asian, american hispanic, other.
AEs, most of which were mild in severity and unrelated to study drug administration, were reported in 18% of patients in each treatment group. Pyrexia was the most commonly reported AE at 4% in each group. Bronchospasm, postprocedural pain, and diarrhea were the next most common AEs, at 1%–2% in each group.

Eleven patients experienced AEs considered to be possibly related to the study drug: five (1.5%) in the placebo group and six (1.8%) in the ondansetron group. Agitation was reported for two placebo-treated and three ondansetron-treated patients. Other study drug–related AEs, occurring in one patient each, were tachycardia, skin redness, and excessive crying in the placebo group and nonspecific swelling, swelling of the face and eye, and aggressive behavior in the ondansetron group.

Two ondansetron-treated patients had serious AEs (SAEs; hypocapnia, hypoxia, and nodal arrhythmia in one patient and staphylococcal infection in another), none of which was attributed by the investigator to the study drug. Two placebo-treated patients each had one SAE not attributed to the study drug (bronchospasm and exacerbated pain), and one patient was reported to have one SAE possibly related to the study drug (tachycardia).

There were no apparent differences in the incidence or pattern of AEs between treatment groups.

### Table 2. Summary of Emetic Episodes and Time to First Emetic Event

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Patients with emetic events (primary end-point)</th>
<th>Median time(^b) to first emetic event (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n = 335)</td>
<td>93(^c) (28%)</td>
<td>135 (n = 93(^c))</td>
</tr>
<tr>
<td>Ondansetron (n = 335)</td>
<td>38(^d) (11%)</td>
<td>207 (n = 38(^d))</td>
</tr>
</tbody>
</table>

\(^a\) Odds/hazard ratios <1 indicate superiority of ondansetron over placebo. Odds/hazard ratios are based on the entire population.

\(^b\) \(t = 0\), discontinuation of anesthesia.

\(^c\) Includes only patients counted as having an emetic event; 57 (17%) patients with 1–2 emetic events, 26 (8%) patients with >2 emetic events or received rescue medication or were withdrawn from the study, and 10 (3%) patients with missing/incomplete data.

\(^d\) Includes only patients counted as having an emetic event; 19 (6%) patients with 1–2 emetic events, 9 (3%) patients with >2 emetic events or received rescue medication or were withdrawn from the study, and 10 (3%) patients with missing/incomplete data.

Figure 1. Displays a Kaplan-Meier plot depicting emesis for ondansetron- and placebo-treated patients in the expected opioid and non-opioid strata. Time to first emetic event is defined as the difference in time between the discontinuation of anesthesia and the first emetic event. Subjects who completed the study without experiencing any emetic episodes and without requiring rescue medication(s) were censored at the end of the 24-h postoperative assessment period.
for subgroups based on expected opioid use, age, sex, race, or ASA physical class.

Discussion

Since the introduction of ondansetron in 1991, several placebo-controlled studies have demonstrated its efficacy in preventing PONV or POV in pediatric surgical patients at doses (0.075–0.15 mg/kg IV) comparable to that used in the present study (16–19). Most of these studies included patients younger than two years of age; however, these patients typically constituted only a small portion of the total study population. None of the studies analyzed these patients separately. The results of this study, the first large-scale, placebo-controlled evaluation of the safety and prophylactic postoperative antiemetic effectiveness of ondansetron in patients younger than two years of age, demonstrate that ondansetron (0.1 mg/kg) is well tolerated and effective in preventing POV.

A variety of anesthetic, nonanesthetic, and postoperative factors are thought to be associated with the occurrence of PONV or POV (3,4). Through application of targeted inclusion/exclusion criteria and treatment group stratification, combined with a large study population, several important predisposing factors were controlled in the present study, as evidenced by the comparability of the treatment groups with respect to patient demographic characteristics, nature and duration of surgery, history of motion sickness and POV, and proportion of patients expected to receive (and actually receiving) opioids during anesthesia and after surgery.

In this study, the background incidence of patients exhibiting emesis (i.e., in patients receiving placebo) was 28%. The computation of incidence included not only patients with actual emetic episodes during the observation period, but also those who prematurely withdrew from the study or received rescue medication (before emesis or in the absence of emesis) or who had incomplete or missing data (Table 2). When incidence was calculated using only patients who actually experienced an emetic event, the percentages of patients with emesis in the placebo and ondansetron groups were 23% and 7%, respectively. The value of 23% for background incidence of emesis in this study for the total patient population, 1- to 24-months-old, is consistent with data by Rowley and Brown (7) showing incidences of POV in the range of 20%–30% in children 1–3 years of age and the value of 20% for 1- to 2-year-old patients reported by Schreiner et al. (13).

Analysis of the incidence of emesis by age category revealed comparable background (placebo) incidences for 1- to 12-month-old patients (27%) and 13- to 24-month-old patients (28%). The incidence of emesis in the youngest age group was unexpected, given the frequently held view that within the pediatric population, the incidence of POV increases with age (3,4,13). In their survey of pediatric surgical patients, Schreiner et al. (13) reported incidences of POV of <10% in children one year or younger in age and approximately 20% in children one to two years of age.

In our study, ondansetron was effective when administered to pediatric patients before the start of surgery. Compared with placebo, ondansetron given before surgery resulted in significantly fewer patients exhibiting emesis and delayed onset of emesis in those who did exhibit emesis. Fewer ondansetron-treated patients required rescue medication, and less emesis was observed after rescue medication when compared with placebo. This study demonstrates that ondansetron, given before surgery, leads to a significant reduction in the risk of POV and enhances the effectiveness of rescue medication in children who require postoperative control of emesis.

Drs. Roth, Cohen, Simhi, Bolos, and Brooks enrolled patients in this study in collaboration with the principal investigators, Drs. Côté, Hannallah, Davis, Khalil, and Ansermino, respectively. The medical writing and editorial assistance of James Neal Weakly, PhD, and Marian Saxon Rhodes, PhD, of Lineberry Research Associates, L.L.C. is greatly appreciated.

References