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Intravenous Ondansetron in Established Postoperative Emesis in Children

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Background: **In pediatric postsurgical patients, postoperative vomiting is a common occurrence that can delay recovery and result in unplanned hospital admissions after outpatient surgery. This randomized, double-blind, placebo-controlled, multicenter study evaluated the efficacy and safety of ondansetron in the control of established postoperative emesis in outpatients aged 2–12 yr.**

Methods: **Screened for the study were 2,720 ASA physical status 1–3 children undergoing outpatient surgery during general anesthesia, which included nitrous oxide. Children experiencing two emetic episodes within 2 h of discontinuation of nitrous oxide were given intravenous ondansetron (n = 192; 0.1 mg/kg for children weighing ≤40 kg; 4 mg for children weighing >40 kg) or placebo (n = 183).**

Results: **The proportion of children with no emetic episodes and no use of rescue medication was significantly greater ($P < 0.001$) in the ondansetron group compared with placebo for both 2- and 24-h periods after study drug administration (78% of the ondansetron group and 34% of the placebo group for 2 h; 53% of the ondansetron group and 17% of the placebo group for 24 h). Among patients with at least one emetic episode or with rescue medication use, the median time to onset of emesis or rescue was 127 min in the ondansetron group compared with 58 min in the placebo group ($P < 0.001$). The median time from study drug administration until discharge was significantly shorter ($P < 0.01$) in the ondansetron group (153 min, range 44–593 min) compared with the placebo group (173 min, range 82–622 min). The incidence of potentially drug-related adverse events was similar in the ondansetron (3% of patients) and the placebo (4% of patients) groups.**

Conclusion: **A single dose of ondansetron (0.1 mg/kg up to 4 mg) is effective and well tolerated in the prevention of further episodes of postoperative emesis in children after outpatient surgery. Administration of ondansetron also may result in a shorter time to discharge. (Key words: Complications, postoperative: emesis; nausea. Pharmacology: ondansetron. Surgery: pediatric.)**

NAUSEA and vomiting are among the most commonly occurring complications after surgery.[1–3] The overall incidence of postoperative nausea and vomiting among children has been reported to exceed 40%.[3] After procedures such as strabismus surgery, the incidence in pediatric patients may approach 90%.[2]

The consequences of postoperative emesis range from extensive discomfort for the patient to health threats

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such as electrolyte imbalance and dehydration.[1,4] Postoperative emesis and the complications arising from it may delay recovery during the acute postsurgical period. In both children and adults, postoperative nausea or emesis has been shown to be a major reason for unexpected hospital admission.[5–7] Emesis-related hospital admission or prolongation of recovery room stay may cause both the patient and the institution to incur additional cost. However, prophylactic administration of antiemetics may not be appropriate or cost effective for all patients.

The availability of an effective, well-tolerated antiemetic agent is particularly important for children undergoing procedures in which the incidence of postoperative emesis is known to be high. The selective serotonin ($5\text{-}HT_3$) antagonist ondansetron is effective in the prevention of postoperative emesis in adults[8–12] and the prevention of chemotherapy-induced emesis in children.[13] Previous studies of ondansetron in pediatric surgical patients have focused on the prevention of postoperative emesis.[14–17] This double-blind, randomized, placebo-controlled study evaluated the safety and efficacy of ondansetron as therapy for established postoperative emesis in children after outpatient surgery under nitrous oxide-based general anesthesia.

Materials and Methods

Patients

ASA physical status 1–3 patients aged 2–12 yr scheduled to undergo outpatient surgery involving general anesthesia were eligible for the study. Children must have experienced two emetic episodes within 2 h of discontinuation of nitrous oxide to be randomly assigned to treatment with a study drug. An emetic episode was defined as a single episode of vomiting (expulsion of any stomach contents through the mouth) or retching (attempts to vomit not productive of any stomach contents) or any number of continuous vomits and/or retches. Children who had received tricyclic antidepressants, monoamine oxidase inhibitors, scopolamine, promethazine, chlorpromazine, Dramamine (Searle, Chicago, IL), metoclopramide, corticosteroids, lorazepam, or phenothiazine within 24 h prior to surgery or who were scheduled to receive any of these medications during the 24-h postoperative period were excluded from the study. Children with known liver or renal disease or with a history of vomiting or retching within 24 h before surgery also were excluded from the study.

Procedures

The protocol for this randomized, double-blind, parallel-group study was approved by the institutional review boards for each of the 43 study sites. All study sites followed the standard protocol and used standard forms for data collection.

Parents or legal guardians of all participating children gave written, informed consent. During the screening visit, which occurred within 7 days of surgery, medical histories were obtained, and physical examinations were performed.

When patients arrived at the facility on the day of surgery, their eligibility for entry into the study was reevaluated. Blood samples for clinical laboratory tests including hematology, clinical chemistry, and renal and hepatic function were obtained. The choice of anesthesia premedication and the method of induction of anesthesia were left to the discretion of the anesthesiologist, except that propofol was excluded. The use of opioids was left to the discretion of the investigator. Anesthesia was maintained with nitrous oxide:oxygen (maximum 70%:30%) and supplemental inhalational agents as needed. Tracheal intubation was optional. Gastric decompression and suctioning were performed on each patient before awakening. Postoperative pain medication was permitted at the discretion of the investigator.

Upon the occurrence of two emetic episodes within 2 h of discontinuation of nitrous oxide, children were assigned to either ondansetron (ondansetron hydrochloride dihydrate, undiluted, 0.1 mg/kg for children weighing ≤40 kg; 4 mg for children weighing >40 kg) or placebo (total volume 0.5 ml/kg to a maximum of 2 ml) according to a computer-generated random code. Blinded study drug was prelabeled with treatment numbers and supplied to each study site by the study sponsor (Glaxo, Research Triangle Park, NC). Study drug was administered intravenously over a period not less than 30 s.

Children were observed in the facility for at least 2 h after receipt of study drug. Heart rate and blood pressure were assessed immediately before and at specified time points after administration of study drug. In the postanesthesia care unit, study personnel also recorded adverse events, the number of emetic episodes experienced by each child, and any use of concurrent or rescue medication. Rescue antiemetic therapy was administered if a child had three emetic episodes within a 15-min period; a physician ordered it; or a child, parent, or guardian requested it. The choice of rescue

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medication was left to the discretion of the physician, but the use of ondansetron was prohibited. Blood samples for clinical laboratory tests were obtained 2 h after study drug administration. After the patient was discharged, the parent or guardian recorded on a diary card adverse events, emetic episodes, and any use of concurrent or rescue medication throughout the 24-h period after study drug administration. Study personnel also contacted the parent or guardian at the end of the 24-h study period.

Statistical Analysis

All statistical tests were two-sided. P values ≤ 0.05 were considered to be statistically significant. Power calculations revealed that, assuming 75% of placebo patients would continue to vomit, 187 patients per group were required to provide 85% power to show a 15% difference with respect to the proportion of patients with no emetic episodes (ondansetron 40% *vs.* placebo 25%).

T tests were performed to detect between-group differences in the demographic variables age, weight, and height. Chi-square tests were performed to detect between-group differences in gender, ethnic origin, susceptibility to motion sickness, previous anesthetic experience, and type of surgery.

The primary efficacy parameter was the proportion of children with no emetic episodes during the initial 2 h after study drug administration and during the 24-h period after study drug administration. Children who had no emetic episodes and who were not rescued were classified as having complete response. Children who experienced one or more emetic episodes, were rescued, or withdrew from the study were classified as treatment failures. Differences in the proportion of complete response between the ondansetron group and the placebo group were tested with the Mantel-Haenszel test. The two emetic episodes required for study enrollment were not included in the analyses. In addition, the Wilcoxon rank sum test was used to compare the ondansetron group with the placebo group with respect to the number of emetic episodes experienced during the 2- and 24-h periods after study drug administration. Children who required rescue medication or who withdrew from the study for any reason were assigned the same arbitrarily high number (>4) of emetic episodes for this comparison.

Safety parameters included adverse events, vital signs, and the results of clinical laboratory tests. Adverse events were defined as any untoward medical occurrence with the exception of emesis (an efficacy parameter) or regional pain associated with the surgical procedure. Nausea, which was not included as an efficacy measure owing to its subjective nature, could be reported as an adverse event. Fisher's exact test was used to compare the ondansetron and placebo groups with regard to adverse events. A t test was used to compare treatment groups with respect to mean diastolic blood pressure, systolic blood pressure, and heart rate at each assessment period. Pretreatment to posttreatment changes in laboratory test values were evaluated by treatment group in three ways: shifts in relation to normal range, mean laboratory values, and potentially clinically significant laboratory changes.

Results

Patient Disposition and Characteristics

Written, informed consent was obtained from parents or guardians of 2,720 children. Three hundred seventy-five of the 2,720 met eligibility criteria for enrollment in the study. Of these 375, 12 children had protocol violations (*e.g.*, administration of excluded medication, early discharge, outpatient data not available, dose outside of specified bounds) within the first 2 h after study drug administration, and an additional 12 patients had protocol violations after the 2-h period. Thus, 363 children were included in efficacy subgroup analyses for the 2-h period, and 351 patients were included in efficacy subgroup analyses for the 24-h period. All 375 patients meeting eligibility criteria who were randomized to treatment with study drug were included in the intent-to-treat analyses and are the basis of the discussion of results. The number of patients consenting for enrollment in the top ten enrolling sites ranged from 134 to 298 with the actual numbers of children randomized to treatment per site ranging from 12 to 56.

Demographic characteristics did not differ between treatment groups (table 1). Sixty percent of children in each treatment group had no previous anesthetic experience (table 1). The majority of children were reported not to be susceptible to motion sickness (table 1). There was no difference between groups with respect to the distribution of the type of surgery performed; the majority of patients underwent ear/nose/throat or eye surgery (table 1). The median duration of anesthesia was 54 min (range 11–209 min) in the ondansetron group and 54 min (range 7–205 min) in the placebo group (table 1). Fifty-one percent of children in each group received intraoperative opioids.

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Table 1. Demographic and Patient Characteristics

Characteristic	Placebo [n (%)]	Ondansetron [n (%)]
No. of patients	183	192
Mean age, years (SD)	6.0 (2.7)	6.0 (2.8)
Mean weight, kg (SD)	25.4 (12.2)	24.4 (11.1)
Mean height, cm (SD)	118 (18.9)	117 (18.0)
Gender, n (%)		
Male	115 (63)	107 (56)
Female	68 (37)	85 (44)
Ethnicity, n (%)		
White	137 (75)	136 (71)
Black	12 (7)	22 (11)
Hispanic	29 (16)	33 (17)
Asian	3 (2)	1 (<1)
Other	2 (1)	0 (0)
Susceptibility to motion sickness, n (%)		
No	170 (93)	181 (94)
Previous anesthetic experience, n (%)		
None	109 (60)	116 (60)
Without nausea/vomiting	51 (28)	53 (28)
With nausea/vomiting	23 (13)	23 (12)
Frequency and type of surgery, n (%)		
Ear/nose/throat or oral	95 (52)	109 (57)
Eye	52 (28)	43 (22)
Abdominal	15 (8)	18 (9)
Male genital	6 (3)	15 (8)
Peripheral	10 (5)	6 (3)
Orthopedic	5 (3)	1 (<1)
Median duration of anesthesia, min (range)	54 (17–205)	54 (11–209)

Efficacy Data

Two-hour Postdose Period. During the 2-h period after study drug administration, 78% of children in the ondansetron group experienced no emetic episodes and required no rescue medication compared with 34% of the placebo group ($P < 0.001$; table 2). Results for the efficacy subgroup were similar: ondansetron 79% ($P < 0.001$) *versus* placebo 34% ($P < 0.001$). Ondansetron-treated children also experienced fewer emetic episodes compared with placebo-treated patients ($P < 0.001$; table 2). Nine percent of children in the ondansetron group compared with 27% of the placebo group required rescue medication during the 2-h period. The median time to onset of emesis or to use of rescue medication after study drug administration among children who experienced emesis or used rescue medication was 127 min in the ondansetron group compared with 58 min in the placebo group ($P < 0.001$).

Twenty-four-hour Postdose Period. During the 24-h period after study-drug administration 53% of the ondansetron group experienced complete response compared with 17% of the placebo group ($P < 0.001$; table 2). Complete response results were identical for the efficacy subgroup. Ondansetron-treated children also experienced fewer emetic episodes compared with placebo-treated children ($P < 0.001$; table 2). Seventeen percent of the ondansetron group compared with 51% of the placebo group required rescue medication during the 24-h period.

Time to Discharge. Analysis of the time period from study drug administration until discharge from the treatment facility (or from the recovery area if the patient required hospital admission) was performed. The median time to discharge for the ondansetron group was significantly shorter (153 min, range 44–593 min; $P < 0.01$, Wilcoxon rank sum statistic) compared with the time to discharge for the placebo group (173 min, range 82–622 min).

Safety Data

The overall incidence of adverse events was 36% in the ondansetron group and 47% in the placebo group ($P < 0.05$). The overall incidence of adverse events

Table 2. Emetic Episodes and Rescue Medication Use during the 2- and 24-Hour Periods after Study Drug Administration

	Placebo [n (%)]	Ondansetron [n (%)]
2-h postdose period		
N	183	192
Complete response	63 (34)	150 (78)*
Treatment failure	120 (66)	42 (22)
Rescue medication administered	50 (27)	17 (9)
1 episode	53 (29)	16 (8)
2 episodes	14 (8)	8 (4)
3 episodes	2 (1)	1 (<1)
≥4 episodes	1 (<1)	0 (0)
24-h postdose period		
N	179	186
Complete response	30 (17)	98 (53)*
Treatment failure	149 (83)	88 (47)
Rescue medication administered	92 (51)	32 (17)
1 episode	23 (13)	23 (12)
2 episodes	16 (9)	16 (9)
3 episodes	6 (3)	10 (5)
≥4 episodes	12 (6)	7 (4)

* $P < 0.001$ ondansetron group *versus* placebo group for proportion of patients experiencing complete response (no emetic episodes and no rescue medication) and for overall number of emetic episodes for both 2- and 24-h periods.

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considered by the investigator to be potentially related to administration of the study drug was not significantly different between the ondansetron group (3% of patients) and the placebo group (4% of patients). Potentially drug-related headaches were reported in 3% of ondansetron-treated children and 2% of placebo-treated children.

A total of 17 children required unplanned hospital admission. Fourteen children required admission on the day of surgery, 11 of whom (3 in the ondansetron group and 8 in the placebo group) were admitted because of continued nausea and/or vomiting. Six of these children underwent tonsillectomy or adenotonsillectomy and three underwent eye muscle surgery. All 11 children had received alternative rescue antiemetic medications. Four of the placebo-treated children required two or more different antiemetic agents. Three additional children were admitted on the day of surgery because of other surgical complications. Because of the small number of children requiring admission, differences among treatment groups did not achieve statistical significance.

Three children required admission to the hospital on the first postoperative day or later. Two ondansetron-treated children were admitted because of dehydration after tonsillectomy/adenotonsillectomy and one placebo-treated child was admitted because of wound infection.

Changes in vital signs after study drug administration were similar in the ondansetron and placebo groups. Similarly, the results of clinical laboratory tests did not differ significantly among treatment groups.

Discussion

The results of this current multicenter study demonstrate that a single dose of ondansetron (0.1 mg/kg for children weighing ≤40 kg; 4 mg for children weighing >40 kg) is effective and well tolerated as therapy for established postoperative emesis in children after outpatient surgery. During the 2-h period after study drug administration, 78% of ondansetron-treated children compared with 34% of placebo-treated children experienced no additional emetic episodes and did not require rescue medication. During the 24-h period after study drug administration, 53% of ondansetron-treated children compared with 17% of placebo-treated children experienced no additional emetic episodes and did not require rescue medication. In addition, fewer ondansetron-treated children compared with placebo-treated children required rescue medication throughout both the 2- and 24-h postdose periods.

These data complement the results of studies in which ondansetron administered during induction of anesthesia was shown to prevent the occurrence of postoperative emesis.[14–17] For example, in one study involving 200 patients aged 2–10 yr,[14] 10% of patients treated with ondansetron (0.1 mg/kg administered intravenously after the induction of anesthesia) compared with 40% of placebo-treated patients experienced nausea, retching, or emesis during the 4-h period after entry into the postanesthesia care unit. Similar results have been obtained in other studies evaluating the effects of ondansetron administered to prevent postoperative emesis.[15–17] Unlike the current study, these studies evaluating the effects of ondansetron in the prevention of postoperative emesis did not include as an eligibility criterion the requirement that patients experience emesis.

Because the primary focus of this study was to evaluate the effects of ondansetron in children who suffer postoperative nausea and vomiting, strict entry criteria were used. To be eligible to receive study drug in the current study, children had to have experienced two emetic episodes within 2 h of discontinuation of nitrous oxide. Informed parental consent was obtained for a total of 2,720 children. Of these, 375 (14%) met all entry criteria and were randomized to receive study drug. Although the incidence of vomiting appears to be quite low in this population (thus posing the question of the need for antiemetic intervention), the incidence rate actually may be artificially low owing to the stringent entry criteria imposed. No additional data were collected on those children who did not experience the required number of emetic episodes within the 2-h period after nitrous oxide discontinuation and thus who were not randomized to study drug. Had these children also been followed for 24 h, the reported incidence of postoperative emesis would likely have been higher.

During the 24-h period after study drug administration, 83% of placebo-treated children experienced at least one additional emetic episode, were rescued, or were withdrawn after the receipt of study drug. In other studies examining the prevention of postoperative emesis in pediatric patients, high rates of emesis also have been reported in children receiving placebo. In one study,[15] for example, emesis was experienced by 67% of 2–17-yr old strabismus surgery patients treated

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with placebo. In another study,[16] 73% of placebo-treated children experienced postoperative emesis on the day of tonsillectomy with or without adenoidectomy. These two studies are not directly comparable to the current one in that experiencing emesis was not a prerequisite to receiving the study drug, yet all of the studies do report consistently high emesis rates in placebo-treated children. While the occurrence of one emetic episode may not be problematic, continued vomiting could potentially result in a prolonged postanesthesia care unit stay or an unplanned admission.

Like the efficacy data, the clinical safety data from this study complement and extend the results of previous pediatric studies in which ondansetron was administered for the prevention of postoperative emesis.[14–17] In addition, the tolerability of ondansetron in this and other pediatric studies is consistent with that observed in adults given ondansetron for the prevention of postoperative nausea and vomiting.[8–11] The incidence of adverse events, changes in vital signs, and clinical laboratory values did not differ between ondansetron- and placebo-treated children.

In a relatively recent editorial, Fisher[18] questioned whether a reduced incidence of nausea and vomiting was a reasonable endpoint in studies of antiemetics. One of us has previously stated our belief that postoperative nausea and vomiting are not surrogate endpoints[19] and other anesthesiologists support this view.[20] Fisher[18] suggested that more appropriate study endpoints might include the duration of recovery room stay, the incidence of unplanned hospital admissions, and patient satisfaction. The author also suggested that shorter recovery periods may be excellent indicators of the cost effectiveness of treatment.

Despite the 2-h stay required in the current study, the interval between study drug administration until discharge from the treatment facility or recovery area was significantly shorter in children treated with ondansetron compared with children who received placebo. These results differ from those of a previous study[21] that did not demonstrate a difference in the length of hospital stays among children who received prophylactic ondansetron or placebo. In the current study, although not statistically significant, the number of unplanned hospital admissions also was lower in children treated with ondansetron compared with those who received placebo. Although patient or family satisfaction was not assessed in this study, a previous study by Watcha *et al.*[22] reported significantly less vomiting in children who received 50 or 100 μg/kg ondansetron compared with those who received placebo and significantly lower assessment scores for the global perioperative experience by the parents of patients who experienced emesis.

These results suggest that the administration of ondansetron to children with established postoperative vomiting may decrease the length of hospital stays, potentially offsetting the cost of the drug. In the face of current economic concerns, clinicians may choose to wait until the onset of emetic symptoms to initiate therapy. In choosing an antiemetic, consideration must be given to the safety, efficacy, and incremental cost of the drug.

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