Anesthesiology
83:956–960, 1995

Effect of Antiemetic Therapy on Recovery and Hospital Discharge Time

A Double-blind Assessment of Ondansetron, Droperidol, and Placebo in Pediatric Patients Undergoing Ambulatory Surgery

Peter J. Davis, M.D., Francis X. McGowan, Jr., M.D.,† Ira Landsman, M.D.,† Karen Maloney, R.N., B.S.N.,‡ Paul Hoffmann, B.S., R.Ph.§*

Background: **Postoperative nausea and vomiting continue to be a significant problem for pediatric ambulatory surgery patients. Although ondansetron has been demonstrated to be effective in the prophylactic treatment of postoperative nausea and vomiting (surrogate end point) no one has demonstrated a benefit of antiemetic therapy on patient recovery, postanesthesia care unit length of stay, and hospital length of stay (nonsurrogate end points). In a double-blind manner, the effects of ondansetron, droperidol, and placebo on the incidence of emesis, postanesthesia care unit stay, and hospital discharge time were evaluated in children undergoing dental surgery.**

Methods: **The subjects were 102 children aged 2–8 years undergoing complete dental restoration. All patients received midazolam before undergoing inhalational induction of anesthesia with N_2O/O_2 and halothane. Anesthesia was maintained with N_2O/O_2 and alfentanil. Patients were then randomized to receive ondansetron (0.1 mg/kg), droperidol (75 μg/kg), or placebo (normal saline) in a double-blind fashion. At the conclusion of the anesthesia, a trained nurse observer assessed patient recovery and recorded the time patients met specified criteria for postanesthesia care unit and hospital discharge as well as episodes of emesis in the hospital and at home during the first 24 hr after surgery.**

Results: **Ninety-five patients completed the study. The three antiemetic groups were similar with respect to age, weight, length of surgery, dose of alfentanil, and route of preanesthetic medication. The 24-hr incidence of emesis was significantly less with ondansetron (9%) than with placebo (35%) or droperidol (32%). Ondansetron-treated patients had significantly shorter hospital stays than droperidol-treated patients, but recovery parameters were similar between the ondansetron- and placebo-treated patients.**

Conclusions: **Ondansetron is an effective prophylactic antiemetic agent for children undergoing dental surgery. Compared with droperidol, ondansetron decreases the length of hospital stay, but compared to placebo, there were no differences in the patient recovery parameters. (Key words: Anesthesia, outpatient: pediatric. Anesthetics, intravenous: alfentanil. Complications, postoperative: nausea; vomiting. Surgery: dental. Vomiting: antiemetic therapy; incidence.)**

POSTOPERATIVE nausea and vomiting continue to be a significant problem for ambulatory surgical patients and potentially can delay hospital discharge or lead to unexpected hospital admissions and increase hospital cost.[1–4] Although numerous antiemetic therapies have been advocated, they are associated with significant side effects.[5–7] Recently, attention has focused on ondansetron, a selective 5HT3 receptor antagonist, shown in numerous studies to be an effective prophylactic antiemetic agent for both adult and pediatric patients undergoing general anesthesia for surgical procedures considered at increased risk for postoperative emesis.[8–13] However, a recent editorial[14] questioned a specific measure of efficacy as a surrogate end point for other factors that determine a drug's utility. Evaluation of nonsurrogate end points may provide insight into the cost effectiveness of various therapeutic regimens. We evaluated, in a double-blind manner, the antiemetic effects of a single dose of ondansetron in children receiving an opioid-based anesthetic and compared its antiemetic effects with those of droperidol and placebo. We also determined the effects of emesis and prophylactic antiemetics on the patient's recovery from anes-

* Associate Professor of Anesthesia, Critical Care Medicine, and Pediatrics, Department of Anesthesiology.

† Assistant Professor of Anesthesia, Critical Care Medicine, and Pediatrics, Department of Anesthesiology.

‡ Research Study Nurse, Department of Anesthesiology.

§ Pharmacy Supervisor, Pharmacy Department.

Received from the Department of Anesthesiology and the Pharmacy Department, University of Pittsburgh School of Medicine, and the Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania. Submitted for publication March 2, 1995. Accepted for publication July 6, 1995.

Address reprint requests to Dr. Davis: Department of Anesthesiology and Critical Care Medicine, University of Pittsburgh, One Children's Place, 3705 Fifth Avenue at DeSoto Street, Pittsburgh, PA 15213-2583.

thesia, and length of stay in the postanesthesia care unit (PACU) and the hospital.

Methods and Materials

This study was approved by the Human Rights Committee at the Children's Hospital of Pittsburgh, and written informed parental consent was obtained. One hundred two patients aged 2–8 years (ASA physical status 1 and 2) undergoing dental surgery, including complete oral restorations and extractions, were randomly assigned to one of three groups using a computer-generated random number code. All patients were premedicated with either intranasal (0.2–0.3 mg/kg; maximum dose 5 mg) or oral (0.5 mg/kg; maximum dose 15 mg) midazolam. Anesthesia was induced with N_2O/O_2 and halothane by mask. After an intravenous catheter had been inserted, atropine (10 μg/kg) and atracurium (0.5 mg/kg) were administered to facilitate nasotracheal intubation and to control ventilation. After tracheal intubation, patients received either droperidol (75 μg/kg), ondansetron (100 μg/kg), or normal saline intravenously. The study drugs were prepared by the hospital pharmacy in specially labeled syringes and the drugs were diluted in normal saline such that an equal volume per body weight of the study drug was intravenously administered to each patient. Throughout the study, both patients and investigators were blinded to the patient's antiemetic treatment group. After the study drug was administered, the halothane was discontinued and anesthesia was maintained with N_2O/O_2 in a 70:30 mixture and alfentanil 100 μg/kg bolus and 2.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ continuous infusion.

Vital sign increases more than 20% of baseline values (*i.e.*, those values obtained on admission to the hospital) were treated with up to three incremental bolus doses of alfentanil (7–10 μg/kg). If vital sign changes were not controlled after 3 bolus doses administered over a 5-min period, the infusion was increased by 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ to a maximum of 4.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Decreases in vital signs to less than 80% of the baseline value were treated by decreasing the infusion in decrements of 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$. If, after 20 min at a steady infusion rate, there was no significant hemodynamic change, the alfentanil infusion was decreased until some hemodynamic response to the surgical stimulation was noted.

During the anesthesia, any patient whose heart rate decreased by more than 25% of the baseline value was given 0.1 mg of intravenous atropine. Atracurium was administered as needed during the operative procedure. Intravenous fluid management consisted of administration of lactated Ringer's solution in which fluid deficits were corrected over the first 2 hr and maintenance fluids were administered according to body weight.

In all patients, neuromuscular blockade was antagonized with neostigmine and atropine and assessed by neuromuscular monitoring of the train-of-four ratio. No patient in either group received local anesthesia for nerve blocks. In all patients, ventilation was controlled and end-tidal CO_2 was maintained between 35–40 mmHg. The alfentanil infusion was discontinued 10 min before the end of surgery and at the conclusion of surgery the stomach was suctioned *via* an oral gastric tube. Following the discontinuation of the anesthetic agents, a trained nurse observer blinded to the study drug administration assessed patient recovery and the incidence of postoperative emesis. The times from cessation of the anesthetic until the patient first responded (opened eyes or made purposeful movements) and met specified criteria for discharge from the recovery room and the hospital were recorded. Our institution has a two-stage recovery area. The first stage is in the PACU. Once a patient meets the criteria for discharge from the PACU, the second stage of recovery occurs in the ambulatory surgical unit, which is physically separate from the PACU. The criterion for discharge from the PACU was a score of ≥8 on our institution's ten-point PACU score. These criteria have been previously reported.[15] The criteria for hospital discharge were discharge from the PACU and the ability of the child to drink fluids once in the ambulatory unit. The nurse observer continuously monitored each patient in the PACU and ambulatory units. She also recorded the incidence of emesis in the PACU and ambulatory units, and telephoned the parents 24 h later to determine the incidence of emesis at home.

An episode of vomiting was defined as expulsion of any stomach contents through the mouth. An episode of *retching* (i.e., dry heaves) was an attempt to vomit that is not productive of any stomach contents. An emetic episode was defined as a single vomit or retch or any number of continual vomits and/or retches. Continual vomiting and/or retching was defined as two or more vomits and/or retches that occur within 1 min of each other. Patients were administered rescue antiemetic medication, when medically indicated, if three emetic episodes occurred within a 15-min period, or at physician discretion, or at any time on patient or parent request. The choice of rescue antiemetic med-

ication was left to the discretion of the attending anesthesiologist. Because nausea is difficult to quantify in children, it was not assessed.

Fisher's exact test, analysis of variance with the Student Newman Keuls Test for *post hoc* analysis and nonparametric equivalents were used to analyze the data statistically. Significance was considered for $P < 0.05$.

Results

One hundred two patients were enrolled in the study and 95 patients (droperidol, 28; ondansetron, 33; placebo, 34) completed the study. Seven patients were excluded because four required steroids for excessive uvula edema, and three required naloxone for respiratory depression. Four patients were in the droperidol group, 1 patient in the placebo group, and 2 patients in the ondansetron group. There was no difference in age (mean ± SD; 42 ± 21 *vs.* 42 ± 14 *vs.* 44 ± 16 months), weight (15.2 ± 4.0 *vs.* 15.2 ± 3.4 *vs.* 15.9 ± 4.6 kg), duration of surgery (107 ± 32 *vs.* 114 ± 28 *vs.* 100 ± 29 min), or dose of alfentanil (3.2 ± 0.5 *vs.* 2.9 ± 1.1 *vs.* 3.1 ± 1.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$) between the droperidol, ondansetron, and placebo groups, respectively. There was also no difference between the distribution (nasal *vs.* oral) of midazolam administration or gender among the groups.

The times to patient response, the PACU and hospital discharge times, and the incidence of emesis during the 24-hr postoperative period are presented in table 1. Ondansetron significantly reduced the incidence of emesis compared with both droperidol and placebo. Although patients treated with ondansetron had shorter hospital stays than did patients treated with droperidol, no difference in this variable was observed between the ondansetron- and placebo-treated patients. Although the analysis of variance of the PACU data suggested a difference between the groups ($p < 0.048$), the *post hoc* analysis did not reveal significant differences between the groups. Table 1 summarizes the occurrence of emesis in those patients who vomited. Of the 24 patients who experienced emesis, 13 patients (54%) had emetic episodes while in the hospital, and 11 patients (46%) had emetic episodes only at home. Of the 95 patients, one patient was readmitted to the hospital because of excessive emesis and dehydration. This patient had received droperidol.

Discussion

Evidence about the efficacy of antiemetic therapies in children is conflicting. In a preliminary study reporting summary measures of the effectiveness of ondansetron and droperidol obtained by meta-analysis of 1026 patients in double-blinded randomized controlled clinical trials, Lopez *et al.*[16] noted that ondansetron was substantially more effective than droperidol in reducing the incidence of emesis.[16] In a double-blinded study with 24-hr postoperative follow-up of pediatric adenotonsillectomy patients, Furst *et al.*[8] found that ondansetron significantly decreased the incidence of emesis compared with placebo, droperidol, or metoclopramide. But in another study comparing ondansetron to placebo in children undergoing oto-

Table 1. Measures of Recovery and Incidence of Vomiting after Prophylactic Antiemetic Administration

	Droperidol (n = 28)	Ondansetron (n = 33)	Placebo (n = 34)
Time to response (min)	13 ± 12.6 (8.3–17.7)	8.8 ± 10.8 (5–12.5)	6.1 ± 6.3* (3.9–8.2)
PACU length of stay (min)	39.9 ± 21.8 (31.9–48)	28.6 ± 18.6 (22.2–33.8)	29 ± 19 (22.7–35.2)
Hospital length of stay (min)	106 ± 59 (84.2–128.3)	74 ± 30* (63.8–84.1)	85 ± 53 (63.8–103.8)
Emesis [n (%)]	9 (32)	3 (9)†	12 (35)
Hospital only	2 (7)	1 (3)	4 (12)
Home only	4 (14)	1 (3)	6 (18)
Both hospital and home	3 (11)	1 (3)	2 (6)

Values are mean ± SD (with 95% confidence interval in parentheses).

* Significantly different from droperidol. $P < 0.05$.

† Significantly different from other two groups. $P < 0.05$.

laryngological, dental, and general surgical procedures, Ummenhofer *et al.*[9] noted that prophylactically administered ondansetron was more effective than placebo in preventing emesis only during the first 4 hr postoperatively; no benefit was apparent from 4 to 24 hr postoperatively. However, none of these reports analyzed the effects of vomiting or its therapy on anesthesia recovery and length of hospital stay.

In the current study, the overall incidence of postoperative vomiting in pediatric patients was significantly less with ondansetron than with droperidol (in a dose previously reported in the literature[5] to be effective for postoperative emesis) or placebo. Recovery and length of hospital stay were similar after ondansetron and placebo, but significantly prolonged after droperidol.

Although one might have suspected that decreasing postoperative emesis would have shortened PACU and hospital stays, comparing the placebo to the ondansetron group in the current study does not support this assumption. Why decreasing the incidence of emesis did not result in earlier discharge is unclear. However, this may be explained in part by the lack of a linear relationship of emesis with length of hospital stay and the need for some critical number of vomiting episodes before patient, family, or staff are sufficiently concerned to initiate medical intervention and hence prolong the hospital stay. In addition, approximately 50% of emetic episodes occurred after hospital discharge and therefore, by definition, could not influence length of hospital stay. Further, our requirement that patients drink to be discharged could have masked differences in discharge times between the two groups. Schreiner *et al.*[17] demonstrated that taking and retaining oral fluids unnecessarily delays hospital discharge. However, if oral fluids had not been a part of our hospital discharge criteria, then patients would have been discharged home based on the PACU discharge criterion. Because both hospital and PACU discharge times were similar between the ondansetron- and placebo-treated groups, it is unlikely that oral fluid administration influenced our discharge times. It could also be argued that we did not use a dose-response relationship of individual drugs to optimize the results. Had we used larger doses of ondansetron we might have observed a better effect. Although the doses selected for ondansetron and droperidol have been reported to be effective, more recently Watcha has noted ondansetron to be equally effective at lower doses.[18]

Anesthesiologists are and increasingly will be required to evaluate the benefits and costs of the treatments that they provide. Fisher[14] questioned the use of the number of emetic episodes as the major means of evaluating antiemetic treatments and argues that antiemetic efficacy is a "surrogate end point" for other, more meaningful outcome measures such as patient satisfaction and shorter recovery periods, which might "offset the cost of the drug" and therefore justify its use. Unfortunately, satisfaction is hard to assess in infants and young children, simply because most are nonverbal. Further, discomfort ratings accorded by a blinded (adult) observer can be quite different from those reported by the child patient.[19] In this instance, whose version is most accurate? Few people would argue that vomiting after surgery is unpleasant. Adults have indicated that their major preoperative concern is postoperative nausea and vomiting,§ and a recent report by Watcha *et al.*,[18] notes that satisfaction scores were significantly better for parents whose children did not have postoperative emesis than for those whose children did have emesis. It thus would seem that vomiting might also be an important concern for children.

As rising medical costs add to our financial concerns and cause us to question the adequacy of drug efficacy and safety as the sole end points by which therapies are evaluated, cost-effectiveness analysis has become another important method with which to assess the appropriateness of the usage of certain drugs.[20–25] However, some limitations are posed by assumptions implicit in financial approaches to medical therapy analysis. In this study, it may be incorrect to assume that medical interventions that allow for fewer emetic episodes automatically equate to reduced costs. Although patients in our study were evaluated continuously by a blinded nurse observer who had no clinical responsibilities for patient care, it is likely that in daily clinical practice, without continuous evaluation of patient readiness, PACU and hospital discharge times are more likely affected by the vagaries of such factors as discharge protocols and staff availability than by the typically small differences produced by different drug regimens. The nonpharmaceutical monetary cost of postoperative nausea and vomiting mainly relates to nursing care, but whether or not emesis increases nursing time and expense is unknown. For cancer chemotherapy, nursing costs constitute a small fraction of the total

§ Orkin FK: What do patients want?—Preferences for immediate postoperative recovery (abstract). Anesth Analg 74:S225, 1992.

cost of the management of emesis. In fact, for chemotherapy patients, management of nausea and vomiting consumed relatively small amounts of hospital resources but incurred considerable costs to the patients and their families.[26] Costs to patients and families may be even more relevant for ambulatory pediatric surgery after which parents assume a large share of the child's postoperative care and consequent costs. In addition, as parents become educated to the self-limited nature of postoperative emesis and as parents feel more comfortable caring for the child at home (rather than in the hospital) the length of hospital stay may be further reduced. Thus, measures that improve the child's well-being may be difficult to quantify financially especially when partial costs of the child's care are already being shifted to the family.

Cost-effectiveness analyses are unquestionably important and need to become a standard component of anesthesia practice. Nevertheless, in pediatric settings, where patient satisfaction may be difficult to assess and where parents assume more patient care responsibility, the outcome of such cost-effectiveness analyses must be critically assessed and weighed against what common sense and surrogate end points tell us is the right thing to do for our patients.

In summary, compared with droperidol and placebo, ondansetron reduced the 24-hr incidence of emesis in children after dental surgery. Length of stay in children receiving ondansetron was decreased compared with those receiving droperidol, but not compared with those receiving placebo.

The authors thank student nurse anesthetists Lori Bonello, Karen Galante, and Buffie Shanley, for their help in intraoperative management and in the postoperative assessment of the patients; Laura Dillman, for secretarial support; and Lisa Cohn, for editorial assistance.

References

1. Kapur PA: Editorial: The big "little problem." Anesth Analg 73:243–245, 1991

2. Patel RI, Hannallah RS: Anesthetic complications following pediatric ambulatory surgery: A 3-yr study. ANESTHESIOLOGY 69:1009–1012, 1988

3. Gold BS, Kitz DS, Lecky JH, Neuhaus JM: Unanticipated admission to the hospital following ambulatory surgery. JAMA 262:3008–1010, 1989

4. Cohen MM, Cameron CB, Duncan PG: Pediatric anesthesia morbidity and mortality in the postoperative period. Anesth Analg 70:160–167, 1990

5. Abramowitz MD, Oh TH, Epstein BS, Ruttiman UE, Friendly DS: The antiemetic effect of droperidol following outpatient strabismus surgery in children. ANESTHESIOLOGY 59:579–583, 1983

6. Dupre LJ, Stieglitz P: Extrapyramidal syndromes after premedication with droperidol in children. Br J Anaesth 52:831–833, 1980

7. Bateman DN, Rawlins MD, Simpson JM: Extrapyramidal reactions with metoclopramide. Br Med J 291:930–932, 1985

8. Furst SR, Rodarte A: Prophylactic antiemetic treatment with ondansetron in children undergoing tonsillectomy. ANESTHESIOLOGY 81:799–803, 1994

9. Ummenhofer W, Frei FJ, Urwyler A, Kern C, Drewe J: Effects of ondansetron in the prevention of postoperative nausea and vomiting in children. ANESTHESIOLOGY 81:804–810, 1994

10. Litman RS, Wu CL, Catanzaro FA: Ondansetron decreases emesis after tonsillectomy in children. Anesth Analg 78:478–481, 1994

11. McKenzie R, Kovac A, O'Connor T, Duncalf D, Angel J, Gratz I, Toplin E, McLeskey C, Joslyn A: Comparison of ondansetron versus placebo to prevent postoperative nausea and vomiting in women undergoing ambulatory gynecologic surgery. ANESTHESIOLOGY 78:21–28, 1993

12. Khalil SN, Kataria B, Pearson K, Conahan T, Kallar S, Zahl K, Gillies B, Campbell C, Brahen N, Gilmour I, Templeton D: Ondansetron prevents postoperative nausea and vomiting in women outpatients. Anesth Analg 79:845–851, 1994

13. Raphael JH, Norton AC: Antiemetic efficacy of prophylactic ondansetron in laparoscopic surgery: Randomized, double-blind comparison with metoclopramide. Br J Anaesth 71:845–848, 1993

14. Fisher DM: Surrogate end points. Are they meaningful? ANESTHESIOLOGY 81:795–796, 1994

15. Davis PJ, Cohen IT, McGowan FX, Jr, Latta K: Recovery characteristics of desflurane versus halothane for maintenance of anesthesia in pediatric ambulatory patients. ANESTHESIOLOGY 80:298–302, 1994

16. Lopez A, Mathieu A: Effectiveness of droperidol (D) and ondansetron (O) for the prevention of postoperative vomiting (POV) in pediatric patients. A meta analysis (MA) (abstract). ANESTHESIOLOGY 81:A1351, 1994

17. Schreiner MS, Nicolson SC, Martin T, Whitney L: Should children drink before discharge from day surgery? ANESTHESIOLOGY 76: 528–533, 1992

18. Watcha MF, Bras PJ, Cieslak GD, Pennant JH: The dose-response relationship of ondansetron in preventing postoperative emesis in pediatric patients undergoing ambulatory surgery. ANESTHESIOLOGY 82:47–52, 1995

19. Beyer JE, McGrath PJ, Berde CB: Discordance between self-report and behavioral pain measures in children aged 3 to 7 years after surgery. J Pain Symptom Manage 5:350–356, 1990

20. Bulpitt CJ, Fletcher AE: Measuring costs and financial benefits in randomized controlled trials. Am Heart J 119:766–771, 1990

21. Detsky AS, Naglie IG: A clinician's guide to cost-effectiveness analysis. Ann Intern Med 113:147–154, 1990

22. Pauker SG, Kassirer JP: Decision analysis. N Engl J Med 316: 250–258, 1987

23. White PF, Watcha MF: Are new drugs cost-effective for patients undergoing ambulatory surgery? Anesthesiology 78:2–5, 1993

24. Johnstone RE, Martinec CL: Costs of anesthesia. Anesth Analg 76:840–848, 1993

25. Watcha MF, Smith I: Cost-effectiveness analysis of antiemetic therapy for ambulatory surgery. J Clin Anesth 6:370–377, 1994

26. O'Brien BJ, Rusthoven J, Rocchi A, Latreille J, Fine S, Vandenberg T, Laberge F: Impact of chemotherapy-associated nausea and vomiting on patients' functional status and on costs: Survey of five Canadian centres. Can Med Assoc J 149:296–302, 1993