Anesthesiology
1996; 85:1076–85

The Dose–Response Relation and Cost-effectiveness of Granisetron for the Prophylaxis of Pediatric Postoperative Emesis

Gary D. Cieslak, M.D., Mehernoor F. Watcha, M.D.,† Michael B. Phillips, B.A.,‡ John H. Pennant, F.R.C.A.§*

Background: **Postoperative nausea and vomiting (PONV) may delay discharge from hospital after ambulatory surgery. The antiserotonin agents, ondansetron and granisetron, provide effective prophylaxis against chemotherapy-induced and postoperative nausea and vomiting in adults, but are expensive. We determined the dose–response relation of granisetron and the financial impact of using this drug in preventing PONV after pediatric outpatient surgery.**

Methods: **In a randomized, double-blind, placebo-controlled study, 97 pediatric outpatients received a placebo or 10 or 40 $\mu g \cdot kg^{-1}$ granisetron intravenously during a standardized anesthetic. Episodes of postoperative retching, vomiting, and times to discharge readiness were recorded. A decision analysis tree was used to divide each study group into nine mutually exclusive subgroups, depending on the incidence of PONV, need for rescue therapy, and the side effects of antiemetics. Costs and probabilities were assigned to each subgroup, and the cost-effectiveness ratio was determined by dividing the sum of these weighted costs by the number of patients free from both PONV and antiemetic side effects.**

Results: **Granisetron (40 $\mu g \cdot kg^{-1}$ intravenously) was more effective than a placebo or 10 $\mu g \cdot kg^{-1}$ granisetron in decreasing the incidence and frequency of postoperative emesis, both in the ambulatory surgery center and during the first 24 h. Patients receiving 40 $\mu g \cdot kg^{-1}$ granisetron also had shorter times to discharge readiness compared with those receiving a placebo. Administering this dose of granisetron to all high-risk patients would cost the ambulatory care center an additional $99 (95% CI, range $89–$112) per emesis-free patient if nursing labor costs are excluded and $101 (95% CI, range $91–$113) if nursing costs are included.**

Conclusions: **In this study, 40 $\mu g \cdot kg^{-1}$ intravenous granisetron (but not 10 $\mu g \cdot kg^{-1}$) provided effective prophylaxis in children against PONV compared with a placebo, but at a high cost. The effective dose of granisetron for PONV prophylaxis is higher than the Food and Drug Administration-recommended dose for chemotherapy-induced emesis. (Key words: Anesthesia, ambulatory: pediatrics. Antiemetics: granisetron. Complications: postoperative vomiting. Economics: drugs.)**

POSTOPERATIVE nausea and vomiting (PONV) remains an anesthetic complication that can cause significant patient discomfort, delay discharge from hospital, and even lead to unanticipated hospital admission after ambulatory surgery.[1] Ondansetron, a 5-hydroxytryptamine subtype 3 (5-HT_3) antagonist, is the first of a new class of drugs that decrease the incidence and frequency of PONV in both children and adults. It is effective in a lower dose (50 $\mu g \cdot kg^{-1}$) than the 100–150 $\mu g \cdot kg^{-1}$ doses required to prevent chemotherapy-induced emesis (CIE).[2–4] Granisetron, a new, more selective 5-HT_3 antagonist, also reduces the incidence of PONV in adults and children,[5–9] but dose-ranging data in the pediatric patient population are limited to CIE.[10,11] Granisetron is expensive but effective in a single daily dose in patients undergoing chemotherapy,[12–14] and, thereby, is claimed to be more cost-effective than other antiemetics in this setting.[15] In this randomized, double-blind, placebo-controlled study, we examined dose–response relation, cost-effectiveness, and parental satisfaction with granisetron in the prophylaxis of PONV in children.

Methods

After Institutional Review Board approval, written informed parental consent was obtained for each patient. We studied 97 healthy American Society of Anesthesiol-

* Assistant Professor, Department of Anesthesiology and Pain Management.

† Associate Professor, Director of Pediatric Anesthesia Research.

‡ Medical student, University of Texas Southwestern Medical School.

§ Associate Professor, Department of Anesthesiology and Pain Management.

Received from the Department of Anesthesiology and Pain Management, University of Texas, Southwestern Medical Center, Dallas, Texas. Submitted for publication March 20, 1996. Accepted for publication July 30, 1996. Support by the Ann Rucker Summer Research Fellowship Fund, and the Dept. of Anesthesiology/Pain Management, The University of Texas, Southwestern Medical Center.

Address reprint requests to Dr. Watcha: Department of Anesthesiology and Pain Management, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, Texas 75235-9068. Address electronic mail to: Watcha@utsw.swmed.edu.

ogists (ASA) physical status 1 and 2 children (mean age 5.2 ± 3.1 yr, range 2–16 yr) scheduled to receive general endotracheal anesthesia for outpatient surgical procedures known to be associated with an increased risk for PONV (*e.g.,* strabismus correction, tonsillo-adenoidectomy, or dental procedures).[1,16,17] Patients were excluded from the study if they had recently received a drug with a known antiemetic effect (*e.g.,* phenothiazines, tricyclic antidepressants, or corticosteroids), or if they had a known allergy or other contraindication to the use of any of the inhalation anesthetic, neuromuscular blocking, or antiserotonin drugs.

After a minimum preoperative fast of 3 h for clear liquids and 6 h for milk or solids, all children received 0.5 $mg \cdot kg^{-1}$ of oral midazolam 15–30 min before induction. Anesthesia was then induced with halothane and nitrous oxide in oxygen *via* a face mask, and intravenous access was established. Tracheal intubation was facilitated with 0.1 $mg \cdot kg^{-1}$ vecuronium intravenously. Anesthesia was maintained with 60% nitrous oxide in oxygen, 2 $\mu g \cdot kg^{-1}$ intravenous fentanyl, and 0.5–1.5% isoflurane, adjusted as needed to maintain heart rate and blood pressure within 20% of baseline. Patients received a placebo or intravenous granisetron in a dose of 10 or 40 $\mu g \cdot kg^{-1}$ before surgical incision, in a double-blind fashion, according to a computer-generated random number. The granisetron dose of 10 $\mu g \cdot kg^{-1}$ was chosen because it is the dose recommended in the Food and Drug Administration-approved package insert for the control of CIE. The dose of 40 $\mu g \cdot kg^{-1}$ was chosen because it is the dose used for the prophylaxis of PONV in one pediatric[9] and three adult studies.[6–8] All study drugs were diluted to 2 ml by a hospital pharmacist to maintain the double-blind nature of the study and were administered intravenously for 30 s. At the end of surgery, residual neuromuscular blockade was antagonized with 50 $\mu g \cdot kg^{-1}$ intravenous neostigmine and 10 $\mu g \cdot kg^{-1}$ glycopyrrolate, the stomach was suctioned, and the trachea was extubated when the patient was awake.

In the postanesthesia care unit (PACU), pain was assessed according to a pain scale described by Hannallah *et al.*[18] Severe pain (pain score ≥ 6) was treated with 1–2 $\mu g \cdot kg^{-1}$ intravenous fentanyl, and milder pain (pain score 3–5) was treated with 10–15 $\mu g \cdot kg^{-1}$ oral acetaminophen. The time from the end of surgery to spontaneous eye opening, obeying commands, ambulation, first oral intake, and discharge readiness from both phase 1 and 2 recovery areas were recorded, as well as any episodes of retching or emesis. Discharge criteria consisted of a fully awake child who recognized parents, had normal, stable vital signs, including oxyhemoglobin saturation > 95% in room air, and was free from persistent pain and emesis. Oral intake was permitted but not required before discharge. However, adequate intravenous fluids were administered to correct the preoperative fluid deficits and intraoperative blood losses and to provide for normal maintenance requirements.

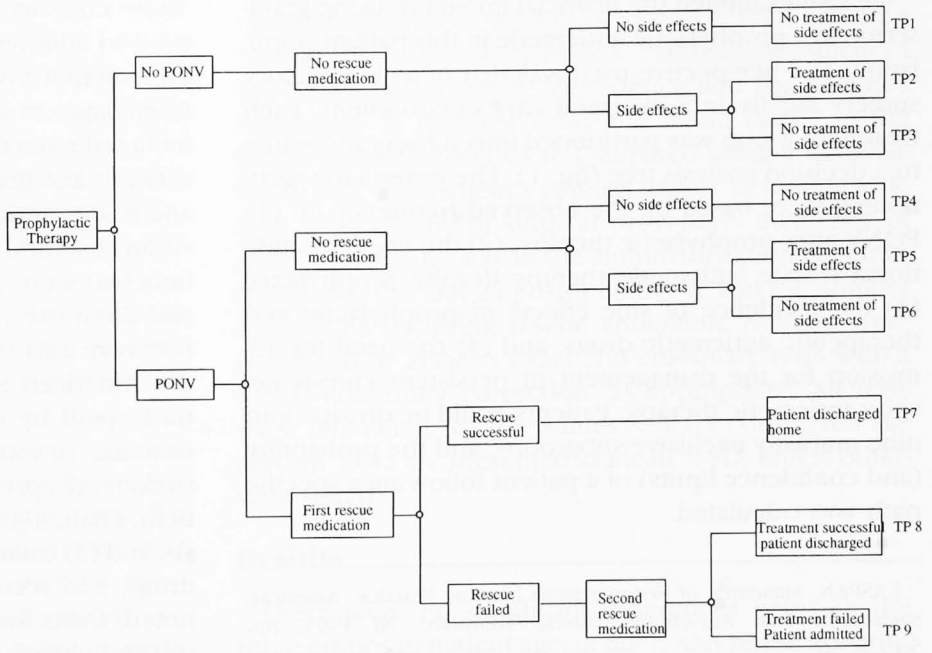

Fig. 1. Decision analysis tree for dividing data sets into nine mutually exclusive subgroups (tree paths TP 1–9). The costs for each subgroup are assigned along with the probabilities of a patient reaching that end-point. The sum of the weighted costs divided by the number of patients without postoperative emesis and the side effects of the antiemetic drugs gives the cost-effectiveness ratio. Reprinted with permission.[38]

Vomiting was defined as the forceful expulsion of gastric contents through the mouth, whereas retching was defined as labored, spasmodic, rhythmic contractions of the respiratory muscles without the expulsion of gastric contents. Both vomiting and retching were considered as emetic episodes. Nausea, a subjective feeling of the urge to vomit, was not evaluated in this study because of the young age of the patients. Patients with emesis before discharge received 0.1 $mg \cdot kg^{-1}$ intravenous metoclopramide as rescue antiemetic therapy. The protocol permitted the administration of other antiemetics, including 25 $\mu g \cdot kg^{-1}$ intravenous droperidol, at the discretion of the attending anesthesiologist, if emesis persisted.

Record was made of all emetic episodes (vomiting and retching) in the hospital. Twenty-four hours after surgery, the investigators, who remained blinded to the study group assignment, conducted followup interviews *via* telephone to determine the incidence of postdischarge emesis and other adverse side effects, as well as any need for analgesic, antiemetic, or other medication at home. Times to first oral intake of fluids and solid food were determined, and the primary caretaker was asked to assess the child's satisfaction with the first solid meal after the operation, using an 11-point scale (from 0 = poor to 10 = excellent). The parent was asked to provide a rating on the same scale of their overall satisfaction with the perioperative experience.

Cost-effectiveness Analysis

We also examined the financial impact of using granisetron as a prophylactic antiemetic in this patient population. The perspective used was that of an ambulatory surgery facility in a managed care environment. Each treatment group was partitioned into subsets according to a decision analysis tree (fig. 1). The criteria for partitioning were based on the observed frequency of: (1) PONV after prophylactic therapy, (2) the need for additional rescue antiemetic therapy despite prophylaxis, (3) the incidence of side effects of prophylactic and therapeutic antiemetic drugs, and (4) the need for admission for the management of persistent emesis despite antiemetic therapy. Patients could be divided into nine mutually exclusive subgroups, and the probability (and confidence limits) of a patient following a specific path was calculated.

Table 1. Basis for Calculations of Mean Costs Associated with Outcomes of Subgroups (Tree Paths TP 1–TP 9) of Figure 1

Outcome	Basis of Calculated Costs for This Outcome
TP 1	Costs of prophylactic antiemetic
TP 2	Sum of the costs of (a) prophylactic antiemetic, (b) side effects of antiemetics, and (c) treating side effects
TP 3	Sum of costs of (a) prophylactic antiemetic, and (b) side effects
TP 4	Sum of costs of (a) prophylactic antiemetic and (b) emesis cleanup
TP 5	Sum of the costs of (a) prophylactic antiemetic, (b) emesis cleanup, (c) side effects, and (d) treating side effects
TP 6	Sum of the costs of (a) prophylactic antiemetic, (b) emesis cleanup, and (c) side effects
TP 7	Sum of the costs of (a) prophylactic antiemetic, (b) emesis cleanup for >1 episode, and (c) rescue antiemetic
TP 8	Sum of the costs of (a) prophylactic antiemetic, (b) emesis clean up for ≥2 episodes, and (c) two doses rescue antiemetics
TP 9	Sum of the costs of (a) prophylactic antiemetic, (b) emesis clean up for >2 episodes, (c) two doses rescue antiemetics, and (d) hospitalization

Costs for reaching a given end-point in the decision analysis tree were assigned and weighted by the probability of a patient reaching that end-point. The basis for assigning costs to each end-point are shown in table 1. These costs included the acquisition cost and materials used to administer prophylactic drugs, along with the incremental costs for the time, drugs, and materials used to manage emesis. Costs for the management of emesis included costs for "emesis clean up," rescue antiemetic therapy, and management of side effects of prophylactic and rescue antiemetic therapy (table 2). The drug acquisition costs and the prorated hourly nursing salary (with benefits) were provided by the hospital administration, and the nurse-patient ratios in the PACU and phase II recovery area were in keeping with the guidelines of the American Society of Postanesthesia Nurses.‖ The time spent by nurses in (1) providing, emptying, and cleaning emesis basins, suction tubing, and Yankauer suckers, (2) providing mouth wash, comforting the patient, changing patient linen and bed clothes after emesis, and (3) calling a physician, administering antiemetic drugs, and recording these events in the chart, were noted. Costs for managing emesis after discharge from the ambulatory surgery center were limited to costs of

‖ ASPAN: Standards of Perianesthesia Nursing Practice. American Society of Post Anesthesia Nurses, Thorofare, NJ 1995, pp. 5,19,47,56.

Table 2. Costs Used in the Cost-effectiveness Analysis

Category of Costs	Costs Used in Study ($)
Antiemetic drug costs	
Granisetron	133 for 1-mg vial
Metoclopramide	2.00 for 10-mg vial
Droperidol	2.50 for 2.5-mg vial
Ondansetron	14.00 for 4-mg vial
Hospitalization costs	1,200 for 24-h hospitalization
Emesis clean-up costs per episode	
Materials	
Inhospital costs	2.50
Postdischarge	0.50
Nursing labor	
In PACU	15.00 (based on 1 nurse: 1 patient)
In phase II recovery	3.75 (based on 1 nurse: 3 patients)
Postdischarge	0
Housekeeping labor:	
In hospital	1.85
Postdischarge	0
Side effects of antiemetic drugs	
Extrapyramidal signs	
Nursing labor	7.50
Drugs	2.69 for diphenhydramine
Drowsiness	
Nursing labor	15 if in PACU, $7.50 if in phase II
Postdischarge	0
Headache	0.05 for acetaminophen
Constipation	0.50 if treated

PACU = Postanesthesia care unit.

materials taken home from the medical care facility and used in cleaning up emesis, along with the costs for antiemetic drugs, and any admission to hospital. Because the cost analysis was performed from the perspective of the institution, indirect costs (lost wages, costs of travel to a pharmacy, physician, or hospital) were not included.

In determining the cost-effectiveness ratio, the sum of the weighted costs associated with that specific dose of granisetron was used as the numerator and therapeutic success as the denominator. Therapeutic success was defined as the number of patients free from emesis and from side effects of antiemetic drugs. Because sampling error was present in both the numerator and the denominator, the 95% confidence intervals for the cost effectiveness ratio were obtained using Fieller's theorem.[19] Sensitivity analysis was performed to determine the effect of varying the probabilities used in partitioning the data and the effect of excluding nursing labor costs on the overall conclusions of the relative cost-efficacy of antiemetic drugs.

It was suggested that a strategy of treating patients with emetic symptoms may be more cost-effective than prophylactic therapy for all. We compared the estimated cost-effectiveness ratios of strategies where granisetron was used for all outpatients and when its use was limited to a rescue antiemetic in the PACU. For the purposes of this comparison, we assumed that the efficacy of granisetron as a prophylactic and rescue antiemetic were similar.

Statistical Methods

The primary measure of efficacy in the study was freedom from postoperative emetic symptoms. A group size of 31 was determined by power analysis for this end-point, based on the assumptions that the incidence of emesis for the placebo and granisetron groups would be similar to a previous placebo-controlled study of ondansetron in the same patient population (58% and 20% for placebo and the treatment group, respectively),[3] and $\alpha = 0.05$, $\beta = 0.2$. The Mantel-Haenszel test was used to compare each of the granisetron groups with the placebo group with regard to the number of patients free from emesis while in the ambulatory surgery center and during the entire 24-h postoperative period. The age, weight, duration of surgery and anesthesia, times from the end of surgery to tracheal extubation, arrival in the recovery area, eye opening, response to commands, and time to discharge were compared between the three groups by analysis of variance, with Scheffe's test for intergroup comparisons. Parental assessment of the global perioperative experience and the patient's enjoyment of the first solid and liquid intake in the postoperative period were compared using a Kruskall-Wallis test. The patient's gender, history of motion sickness, PONV, type of surgical procedure, incidence of emesis during the stay in the ambulatory surgery center and during the first 24 postoperative h, and the number of patients requiring rescue antiemetic therapy were compared by Fisher's exact and chi-square tests with a Yates' continuity correction, as appropriate. All tests were two-tailed, with P values < 0.05 considered significant. Data are presented as mean ± SD, unless otherwise stated.

Results

There were no significant differences between the three groups in patient age, gender, ASA physical status,

Table 3. Demographic, Intraoperative, and Postanesthetic Recovery Data for the Three Treatment Groups

Group	Placebo	Granisetron 10 μg/kg	Granisetron 40 μg/kg
Number (n)	31	33	33
Age (yr)	5.6 ± 3.4	5.5 ± 3.2	4.5 ± 2.8
Gender M/F	18/13	19/14	13/20
ASA physical status 1/2	26/5	22/11	23/10
Weight (kg)	22.0 ± 10.7	23.4 ± 18.9	17.6 ± 7.6
Operation			
Tonsillo-adenoidectomy	5	7	7
Strabismus correction	12	14	15
Dental rehabilitation	12	12	9
Other eye and ENT cases*	2	0	2
Duration of surgery (min)	64 ± 53	45 ± 25	49 ± 35
Duration of anesthesia (min)	86 ± 55	75 ± 24	81 ± 36
PACU arrival (min)	14 ± 10	14 ± 8	13 ± 5
Spontaneous eye opening (min)	38 ± 25	26 ± 17	29 ± 16
Response to commands (min)	43 ± 19	37 ± 25	47 ± 23
First oral intake (min)	171 ± 175	143 ± 141	92 ± 51
Phase I recovery stay (min)	66 ± 39	64 ± 37	61 ± 25

* Includes myringoplasties, tympano-mastoid ectomy.

ASA = American Society of Anesthesiologists; ENT = ear, nose, throat; PACN, postanesthesia care unit.

weight, type of surgical procedure, or history of previous PONV (table 3). The patient groups also exhibited no significant differences in perioperative analgesic requirements, duration of surgery or anesthesia, or times to eye opening, oral intake, or ambulation. In patients who underwent surgeries for strabismus correction, there were no significant differences between groups in the number of eye muscles operated on or the number of operations that involved the inferior oblique muscle.[17]

Patients who received 40 $\mu g \cdot kg^{-1}$ intravenous granisetron had significantly lower incidence of emesis while in the ambulatory surgery center and during the first 24-h postoperative period, compared with patients in the placebo and 10 $\mu g \cdot kg^{-1}$ groups (table 4). In contrast, the number of incidences of emesis when the patient was in the ambulatory surgery center and during the first 24 postoperative hours was not significantly different between the placebo and 10 $\mu g \cdot kg^{-1}$ groups. In the group that received 40 $\mu g \cdot kg^{-1}$ granisetron, 91% of patients were free from emesis during the entire 24-h postanesthesia period, compared with only 58% and 67% of the patients in the placebo or 10 $\mu g \cdot kg^{-1}$ groups, respectively. Among the patients who did vomit, fewer emetic episodes were noted in the 40 $\mu g \cdot kg^{-1}$ group than in the placebo or 10 $\mu g \cdot kg^{-1}$ groups.

Patients who received 40 $\mu g \cdot kg^{-1}$ granisetron had significantly shorter times to discharge readiness when compared with patients in the placebo or 10 $\mu g \cdot kg^{-1}$ groups. There were no significant differences between the placebo and 10 $\mu g \cdot kg^{-1}$ groups in times to either discharge readiness or actual discharge. In all treatment groups, patients who received rescue antiemetic therapy had significantly longer stays in the ambulatory surgery center. Parental assessment scores of the child's enjoyment of the first fluid and solid meal intake after returning home were not significantly different between any of the groups. In addition, the parental global evaluation of the perioperative experience did not differ between the three groups. However, significantly more parents stated that their global assessment of the perioperative experience was <10 if their children had more than one episode of emesis. Four patients complained of headache — two in the placebo group and one each in the other two groups.

We estimated that it would cost the ambulatory care center an additional $101 (95% CI, range $91-$113) for every patient free from emesis if 40 $\mu g \cdot kg^{-1}$ intravenous granisetron was administered as a prophylactic antiemetic to all high-risk patients. If the assumption is made that the efficacy of granisetron as a prophylactic and as a rescue antiemetic are similar, a strategy of limiting granisetron use to rescue antiemetic therapy in the PACU would cost the ambulatory surgery center an additional $39 (95% CI, range $27-$69) per emesis-

Table 4. Incidence of Emesis, Discharge Readiness Times, and Global Evaluation of the Perioperative Experience

Group	Placebo	Granisetron (10 μg/kg)	Granisetron (40 μg/kg)
Number	31	33	33
Incidence of predischarge emesis (%)	35%	27%	3%*
Required rescue antiemetic drugs (%)	22%	12%	3%*
Postdischarge emesis (%)	27%	15%	6%
Emesis during first 24 postoperative h (%)	42%	33%	9%*
Severity of emesis over 0–24 postop. hrs			
None (0 episodes/24 h)	58%	64%	91%*
Mild (1 episode/24 h)	6%	21%	3%
Moderate (2 episodes/24 h)	19%	6%	3%*
Severe (≥3 episodes/24 h)	16%	9%	3%
Discharge readiness (min)	152 ± 85	129 ± 56	108 ± 54*
Mean global evaluation score of perioperative experience by the parent	8.8 ± 2.7	9.3 ± 1.7	9.1 ± 2.0
Percentage of patients who gave a global evaluation score of;			
10	78%	83%	85%
8–9	3%	10%	12%
≤7	19%	7%	3%

* $P < 0.05$ *versus* placebo group.
ASA = American Society of Anesthesiologists; ENT = ear, nose, throat; PACN, postanesthesia care unit.

free patient. These conclusions were sensitive to the incidence and severity of postoperative emesis, and were based on a 35% incidence of predischarge emesis, with no admission to the hospital for the management of emesis. The routine use of granisetron for all patients would be associated with cost savings only if more than 70% of all patients had more than one episode of emesis while in the ambulatory care center or if the rate for unexpected admission to the hospital for the management of emesis exceeded 9% (see Appendix).

As expected, these conclusions were also sensitive to the acquisition price of granisetron, the assigned costs for nursing labor, and wastage of drugs. The acquisition costs of granisetron vary widely from country to country, ranging from $21 in Italy,[20] to $57 in the United Kingdom,[21] to $100 in Japan,[9] to $400 in the United States[22] for a 3-mg dose. Nursing labor costs will also vary. In this study, we used nursing labor and granisetron acquisition costs for the United States. Because of the high costs of granisetron in the United States, the incremental nursing costs of managing emetic symptoms before discharge are relatively low.

The incremental nursing costs for managing emesis while the patients were in the ambulatory care center formed a major component of the estimated costs in the placebo group. In contrast, these costs were small in the group that received 40 $\mu g \cdot kg^{-1}$ granisetron, because only 3% (95% CI, range 0.1–6.0%) had emetic symptoms before discharge. If nursing labor costs were excluded from the analysis, the routine use of 40 $\mu g \cdot kg^{-1}$ intravenous granisetron would cost the ambulatory care center an additional $99 (95% CI, range $89–$112) for every patient free from emesis. If it was assumed that the remainder of the vial of granisetron were discarded, the cost-effectiveness ratio would be $332 (95% CI, range $300–$372) if nursing costs were included and $329 (95% CI, range $298–$369) if these nursing costs were excluded.

Discussion

In this study of pediatric surgical outpatients, granisetron was shown to significantly reduce the incidence of PONV compared with a placebo when administered in a dose of 40 $\mu g \cdot kg^{-1}$ intravenously, but not in a dose of 10 $\mu g \cdot kg^{-1}$. The effective dose of granisetron for prophylaxis of PONV in children in our study was similar to that reported in adults.[5–7] Although 40 $\mu g \cdot kg^{-1}$ intravenous granisetron has been shown to be a more effective prophylactic antiemetic than placebo in a pediatric surgical patient population,[9] dose-ranging data are limited to the management of CIE. Pinkerton *et al.*[23] showed that 10 $\mu g \cdot kg^{-1}$ intravenous granisetron was as effective as 20 and 40 $\mu g \cdot kg^{-1}$ in preventing CIE. Our study showed that this dose (10 $\mu g \cdot kg^{-1}$) was inef-

fective in the prophylaxis of pediatric PONV. It is possible that a dose of granisetron between 10 and 40 $\mu g \cdot kg^{-1}$ may be as effective as the higher dose in the prophylaxis of PONV in children. In comparison, ondansetron is effective in reducing the incidence of PONV at a smaller dose than that used to treat chemotherapy-associated emesis.[3] A possible explanation for the differences in relative potency of the 5-HT_3 receptor antagonists for PONV and CIE is that many factors other than 5 HT_3 receptor stimulation affect PONV, including activation of μ-opioid receptors. Ondansetron is less selective than granisetron in binding to 5-HT_3 receptors, with detectable binding at 5-HT_{1B}, 5-HT_{1C}, 5-HT_3, α-adrenergic, and μ opioid receptor sites.[24,25] If studies with other highly selective 5 HT_3 receptor antagonists, such as dolasetron and RS 25259 (Syntex), also demonstrate similar differences in their relative potency for PONV and CIE, we can speculate that highly selective 5 HT_3 antagonists may be needed in higher doses for the prophylaxis of PONV compared with CIE. If our speculation proves correct and the costs of this group of drugs remain high, we may anticipate an increasing budgetary impact on anesthetic costs with the use of more selective 5 HT_3 receptor antagonists in managing PONV.

One of the cost advantages claimed for the use of granisetron for the prophylaxis of emesis is a prolonged duration of action with a single dose. In patients who received highly emetogenic chemotherapy, a single dose of granisetron had an efficacy comparable with multiple doses of ondansetron.[14,26] In our study and other adult studies of PONV,[5,6] a single intravenous granisetron dose of 40 $\mu g \cdot kg^{-1}$ was associated with decreased emesis during the entire 24-h postanesthetic period. However, a similar prolonged efficacy in preventing PONV was noted with the prophylactic use of single doses of ondansetron and droperidol.[2,27] These findings suggest that cost data from studies of CIE may not apply to PONV.

Another benefit claimed to accompany the use of 5-HT_3 antagonists as compared with droperidol is the absence of sedative side effects.[28] In our study, there were no significant differences in the incidence of side effects among the three groups. There were also no significant differences between the three groups in the times to tracheal extubation, eye opening, orientation, ambulation, or oral intake. These data indicate that the use of granisetron (like ondansetron[28]) is not associated with a dose-related increase in sedative effects. Davis *et al.*[28] reported similar times to awakening in children who received ondansetron or a placebo during dental surgery with a nitrous oxide-alfentanil anesthetic technique. However, these authors failed to demonstrate differences in times to discharge in the patients who received ondansetron or a placebo, although both groups had shorter hospital stays than patients who received droperidol. The time of actual discharge from the ambulatory surgery center depends on a number of factors that are not related to the medical condition of the patient (*e.g.*, completion of all paperwork, availability of the attending surgeon to discuss discharge instructions, availability of transportation home).[29] In studies of sedative effects of antiemetics, it may be more appropriate to examine the time to home-readiness rather than the time of actual discharge from the ambulatory surgery center. In studies of the cost-effectiveness of antiemetics that include nursing labor costs, the time of actual discharge may be more important. In our study, the times to home-readiness were significantly shorter in the group that received 40 $\mu g \cdot kg^{-1}$ granisetron. Changes in nursing practices and the avoidance of protocols that mandate a minimum stay in the postoperative period may result in a closer relation between times to home-readiness and actual discharge.

In keeping with the current movement toward "value-based anesthetic care,"[30] we also examined the value associated with the use of prophylactic granisetron, rather than concentrating on the surrogate endpoint of decreased emesis as the major factor in determining the use of granisetron in outpatient anesthesia.[16] Comparisons of acquisition costs of drugs without regard to the overall outcome or associated side effects are shortsighted, and may not result in true cost savings. Therefore, we examined all costs associated with the management of emesis. We also chose not to use hospital charges for drugs, but rather an estimate of actual costs in the comparisons, because there are major differences between costs and charges.[31] In the model we used, it would cost $101 to prevent one case of PONV, and the expenses to the health-care institution could be justified only if a large number of children had persistent emesis while in the ambulatory surgical center. This pharmacoeconomic model was based on the best possible scenario for granisetron, including an assumption that there would be no wastage of the drug. However, granisetron is available as a preservative-free, single-use vial, and many institutions have a policy of discarding unused drugs 24–48 h after the vial was opened.[32] It would, therefore, be more reasonable to assume there

would be some wastage of granisetron, and the "real world" costs would be even greater than in the model.

Claims of a reduction in associated direct costs with the use of a drug must be subjected to the same scrutiny as any claims of scientific merit.[33] Our model assumed there was a linear relation between the costs of a service and the time spent by personnel in providing this service. From the perspective of the health-care institution, personnel costs are semi-fixed, not variable costs that alter with the amount of time spent by personnel in taking care of a problem.[34] Even if an extra 15–30 min is spent in the ambulatory care center, institutional costs may not be affected. However, if there is a "bottle neck" in the flow of patients through the operating room suites, or if the PACU is working at near capacity, effective prophylactic antiemetic therapy may help reduce the length of stay in the PACU and consequently reduce the need for overtime payments to existing staff or the hiring of additional staff.

Dexter and Tinker[35] stated that the major determinant of PACU economics was the peak number of patients admitted to the PACU. There is a wide seasonal variation in the elective surgical schedule in many pediatric hospitals in the United States, with an increase seen in the summer months. Consequently, PACU staffing requirements and the financial benefits of routine prophylactic antiemetic therapy may be greater to the institution during this period. When the PACU is not working at near capacity, nursing labor requirements may not be altered by a longer PACU stay, particularly if this stay occurs in a physically separate phase II recovery area where parents assist in the care of the child. In this situation, intraoperative antiemetic prophylaxis may not be associated with financial benefits to an institution, although there may be improved patient and parent satisfaction.

Anesthesiology practitioners could use the cost-effectiveness model as a template to construct a cost-effectiveness evaluation that reflects practices in their own institutions if they enter their institutional costs, incidence of emesis, and side effects of antiemetics in tables 1 and 2 and figure 1. We have provided cost-effectiveness ratios both with and without nursing labor costs. Practitioners should examine PACU utilization rates and nursing practices in their own institution, and may choose to add nursing labor costs for days when the PACU is working at capacity and exclude these costs at other times in their cost-effectiveness analysis.

The model also can be used to determine the cost-effectiveness of other antiemetics, such as ondansetron. In a previously published study,[3] the incidence of emesis predischarge, postdischarge, and during the first 24 postoperative hours were 9%, 12%, and 19%, respectively, in patients who received 50 $\mu g \cdot kg^{-1}$ intravenous prophylactic ondansetron. Using the model described earlier, the costs per patient free from emesis and side effects of antiemetic therapy would be \$15 (95% CI, range \$11–\$22) if nursing costs were included and \$9 (95% CI, range \$7–\$12) if these costs were excluded. If the remainder of the vial of ondansetron were wasted, the cost-effectiveness ratio would be \$32 (95% CI, range \$25–\$47) if nursing costs were included and \$26 (95% CI, range \$20–\$38) if these costs were excluded. The validity of using these values and the values from the current study for a direct comparison of the cost-effectiveness of ondansetron and granisetron may be questioned, because the two studies were performed at different times. A prospective comparative study, in which patients are randomized to the ondansetron and granisetron treatment groups, still needs to be performed, to determine their relative efficacy and cost-effectiveness in the prophylaxis of PONV.

Decisions regarding drug usage should not be limited to cost considerations but should include input from patients regarding their preferences. Patients undergoing chemotherapy have reported high satisfaction and a preference for antiemetic regimens with granisetron rather than ondansetron or the more traditional antiemetics.[26] However, such data may not be applicable to the surgical patient population, because the severity of emesis and incidence of the side effects of traditional antiemetic drugs is greater for CIE than for PONV. A possible objection to our analysis is that it assumed the value of avoiding emesis was the same as the value of avoiding the side effects of emesis.[36] Although there are suggestions# that health-care professionals would be willing to tolerate some degree of pain, drowsiness, and delayed discharge to avoid PONV if they were to undergo surgery, there are no data from actual patients or from the parents of pediatric patients.

We failed to demonstrate a higher level of global satisfaction with the perioperative experience in the parents of children who received an effective dose of granisetron compared with a placebo. This failure may represent a type II error rather than a lack of sensitivity of the method used to measure satisfaction or differences

Orkin FK: What do patients want? Preferences for immediate recovery (Abstract). Anesth Analg 1992; 74(Suppl):S225.

between adults and pediatric patients in concerns about PONV. It was suggested that comparisons of patient assessment of medical care should be based on proportions of patients who rated their care as excellent.[37] In our study, this would be represented by an assessment score of 10. Power analysis suggests that 162 patients would need to be recruited into each group to detect a 12% difference (from 78% to 90%) in the proportion of patients with this parental satisfaction score of 10 ($\alpha = 0.05$, $\beta = 0.2$). In our study, a greater proportion of parents assessed the global satisfaction scores to be less than 10 if their child had more than one episode of emesis.

In summary, we demonstrated that granisetron in a dose of 40 $\mu g \cdot kg^{-1}$ (but not 10 $\mu g \cdot kg^{-1}$) is effective in the prophylaxis of PONV in children undergoing outpatient surgery. Additional studies are necessary to determine whether doses between 10 and 40 $\mu g \cdot kg^{-1}$ would be just as effective. However, the high acquisition cost of granisetron makes it difficult to justify its use as a prophylactic antiemetic in the surgical patient population. Future comparative studies of granisetron and other antiemetics should include data on costs, patient satisfaction, and preferences in addition to efficacy data.

The authors thank the nurses and staff of the Children's Medical Center Dallas, for their patience and cooperation during this study. They are extremely grateful to Bill Oden, R.Ph., for the preparation of the study drugs.

References

1. Kenny GNC: Risk factors for postoperative nausea and vomiting. Anaesthesia 1994; 49:6–10

2. Pearman MH: Single dose intravenous ondansetron in the prevention of postoperative nausea and vomiting. Anaesthesia 1994; 49(suppl):11–5

3. 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 1995; 82:47–52

4. Markham A, Sorkin EM: Ondansetron: An update of its therapeutic use in chemotherapy-induced and postoperative nausea and vomiting. Drugs 1993; 45:931–52

5. Mikawa K, Takao Y, Nishina K, Maekawa N, Obara H: The antiemetic efficacy of prophylactic granisetron in gynecologic surgery. Anesth Analg 1995; 80:970–4

6. Fujii Y, Tanaka H, Toyooka H: Reduction of postoperative nausea and vomiting with granisetron. Can J Anaesth 1994; 41:291–4

7. Fujii Y, Tanaka H, Toyooka H: Optimal anti-emetic dose of granisetron for preventing postoperative nausea and vomiting. Can J Anaesth 1994; 41:794–7

8. Fujii Y, Tanaka H, Toyooka H: Granisetron-dexamethasone combination reduces postoperative nausea and vomiting. Can J Anaesth 1995; 42:387–90

9. Fujii Y, Tanaka H, Toyooka H: Granisetron reduces vomiting after strabismus surgery and tonsillectomy in children. Can J Anaesth 1996; 43:35–8

10. Palmer R: Efficacy and safety of granisetron (Kytril) in two special patient populations: Children and adults with impaired hepatic function. Semin Oncol 1994; 21:22–5

11. Miyajima Y, Numata S, Katayama I, Horibe K: Prevention of chemotherapy-induced emesis with granisetron in children with malignant diseases. Am J Pediatr Hematol Oncol 1994; 16:236–41

12. Perez EA, Gandara DR: The clinical role of granisetron (Kytril) in the prevention of chemotherapy-induced emesis. Semin Oncol 1994; 21:15–21

13. Soukop M: Clinical experience with intravenous granisetron. Anticancer Drugs 1994; 5:281–6

14. Navari R, Gandara D, Hesketh P, Hall S, Mailliard J, Ritter H, Friedman C, Fitts D: Comparative clinical trial of granisetron and ondansetron in the prophylaxis of cisplatin-induced emesis. The Granisetron Study Group. J Clin Oncol 1995; 13:1242–8

15. Johnson N, Bosanquet N: Cost effectiveness of 5-hydroxytryptamine3 receptor antagonists: A retrospective comparison of ondansetron and granisetron. Anticancer Drugs 1995; 6:243–9

16. Watcha MF, White PF: Postoperative nausea and vomiting: Its etiology, treatment and prevention. ANESTHESIOLOGY 1992; 77:162–84

17. Lerman J: Surgical and patient factors involved in postoperative nausea and vomiting. Br J Anaesth 1992; 69(suppl 1):24S–32S

18. Hannallah RS, Broadman LM, Belman AB, Abramowitz MD, Epstein BS: Comparison of caudal and ilio-inguinal/ilio-hypogastric nerve blocks for the control of post-orchidopexy pain in pediatric ambulatory surgery. ANESTHESIOLOGY 1987; 66:832–4

19. Sacristan JA, Day SJ, Navarro O, Rose J, Hernandez JM: Use of confidence limits and sample size calculations in health economic studies. Ann Pharmacother 1995; 29:719–25

20. Roila F, Ballatori E, Delfavero A: Antiemetic properties of granisetron—Reply. N Engl J Med 1995; 332:1653–4

21. Jones AL, Lee GJ, Bosanquet N: The budgetary impact of 5-HT3 receptor antagonists in the management of chemotherapy-induced emesis. Eur J Cancer 1993; 29A:51–6

22. Kattlove H: Antiemetic properties of granisetron [letter]. N Engl J Med 1995; 332:1653

23. Pinkerton CR, Jacobson SJ, Leclerc JM, Cohn R, Cedar E: IV granisetron in children receiving highly emetogenic chemotherapy: A double blind dose-ranging study [abstract]. Eur J Cancer 1993; 29A:S200 (abstract 1118)

24. van Wijngaarden I, Tulp MTM, Soudijn W: The concept of selectivity in 5 HT receptor research. Eur J Pharmacol 1990; 188:301–12

25. Ito H, Akuzawa S, Tsutsumi R, Kiso T, Kamato T, Nishida A, Yamano M, Miyata K: Comparative study of the affinities of the 5-HT3 receptor antagonists, YM060, YM114 (KAE-393), granisetron and ondansetron in rat vagus nerve and cerebral cortex. Neuropharmacology 1995; 34:631–7

26. Noble A, Bremer K, Goedhals L, Cupissol D, Dilly SG: A double-blind, randomised, crossover comparison of granisetron and ondansetron in 5-day fractionated chemotherapy: Assessment of efficacy, safety and patient preference. The Granisetron Study Group. Eur J Cancer 1994; 30A:1083–8

27. Paech MJ, Paevi TJG, Evans SF: Single-dose prophylaxis for postoperative nausea and vomiting after major abdominal surgery: Ondansetron versus droperidol. Anaesth Intensive Care 1995; 23:548–54

28. Davis PJ, McGowan FX, Landsman I, Maloney K, Hoffmann P: Effect of antiemetic therapy on recovery and hospital discharge time. ANESTHESIOLOGY 1995; 83:956–60

29. Chung F: Recovery pattern and home-readiness after ambulatory surgery. Anesth Analg 1995; 80:896–902

30. Orkin FK: Moving towards value based anesthesia care. J Clin Anesth 1993; 5:91–8

31. Finkler SA: The distinction between costs and charges. Ann Intern Med 1982; 96:102–9

32. Harrison BR, Godefroid RJ: Relative costs of granisetron and ondansetron [letter]. Am J Hosp Pharm 1994; 51:2196–2205

33. Evans RG: Manufacturing consensus, marketing truth: Guidelines for economic evaluations. Ann Intern Med 1995; 123:59–60

34. Lubarsky J: Understanding cost analyses: Part I. A practitioner's guide for economic evaluations. J Clin Anesth 1995; 7:518–21

35. Dexter F, Tinker JH: Analysis of strategies to decrease postanesthetic care unit costs. ANESTHESIOLOGY 1995; 82:94–101

36. White PF, White LD: Cost containment in the operating room: Who is responsible? J Clin Anesth 1994; 6:351–6

37. Ware JE Jr: What information do consumers want and how will they use it? Med Care 1995; 33:JS25–30

Appendix

Scenario 1: Granisetron (40 $\mu g \cdot kg^{-1}$ intravenously) is given to all patients. Assume there is no waste of granisetron. The predischarge, postdischarge, and overall 24-h emesis rates were 3%, 6%, and 9%, with an overall 24-h success rate of 91% (*i.e.*, 100 − 9 = 91%) For each tree point of the decision analysis tree (TP1–TP9), costs (include nursing labor) were assigned as in tables 1 and 2 and weighted by the probability of each tree point. The sum of these weighted costs was $92. The cost effectiveness ratio (total costs divided by success rate of 91%) would be $101.

Scenario 2: Granisetron (40 $\mu g \cdot kg^{-1}$ intravenously) is given only to patients who vomited in the postanesthesia care unit. Again, assume no waste and include nursing costs. The predischarge, postdischarge, and overall 24-h emesis rates would be that of the placebo group (35%, 27%, and 42%, respectively). The 24-h success rate of this strategy would be 58% (*i.e.*, 100 − 42 = 58%). Assume that the emesis rates after patients received rescue granisetron were similar to those in scenario 1. The sum of the weighted costs of tree points TP1 to TP9 (costs multiplied by probability of each tree point) was $23. The cost effectiveness ratio (total costs divided by success rate) would be $39.

Scenario 3: The problem is to find the conditions under which the cost-effectiveness ratio in scenario 2 is greater than the ratio in scenario 1. This will occur only if the numerator in the cost-effectiveness ratio (sum of the weighted costs) increases and/or the denominator (success rate) decreases. If 70% of patients have more than one episode of emesis before discharge, the success rate is 30%, the sum of the weighted costs increases to $31, and the cost effectiveness ratio becomes $103. Alternatively, if the success rate remains unchanged at 58%, but more patients get admitted to the hospital, the weighted costs are increased by the contribution of the product of the probability and costs of TP9, and the cost-effectiveness ratio will change. If the probability of TP9 (unexpected admission rate) increases to 9%, the weighted costs are $61, and cost-effectiveness ratio will be $105.