Cost-Effectiveness Analysis of Ondansetron and Prochlorperazine for the Prevention of Postoperative Nausea and Vomiting

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ABSTRACT

OBJECTIVE: To compare the cost-effectiveness of 2 antiemetic agents, ondansetron and prochlorperazine, for the prevention of postoperative nausea and vomiting (PONV) in patients undergoing total hip replacement or total knee replacement procedures.

METHODS: The cost-effectiveness analysis model was applied to data derived from a previous clinical study conducted in 1995 and 1996. This study involved 78 adult patients (62.8% female and 37.2% male) undergoing total hip replacement or total knee replacement procedures. Patients were enrolled in a randomized, double-blind manner to receive either ondansetron 4 mg intravenously (n=37) or prochlorperazine 10 mg intramuscularly (n=41) immediately upon completion of surgery and were monitored for occurrences of PONV during the subsequent 48 hours. In our analysis, we measured the cost-effectiveness ratio (C/E ratio), defined as the cost per successfully treated patient, for each antiemetic agent using the clinical data obtained from the previous study.

RESULTS: The incidence of PONV and use of rescue antiemetics was significantly greater in the ondansetron group compared with the prochlorperazine group. The mean total costs of PONV management per patient in the prochlorperazine and ondansetron groups were \$13.99 and \$51.98, respectively (based on 2004 average wholesale prices [AWP]). The cost of successfully treating one patient with prochlorperazine and ondansetron was \$31.87 and \$275.01, respectively. One-way sensitivity analysis was performed adjusting the percent efficacy rate of each antiemetic and the drug cost of ondansetron (up to a 50% reduction in AWP). Prochlorperazine remained the dominant strategy across each scenario.

CONCLUSION: The results indicate that prochlorperazine is a more cost-effective antiemetic compared with ondansetron for the prevention of PONV in a mixed gender, adult inpatient population undergoing total joint arthroplasty.

KEYWORDS: Ondansetron, Prochlorperazine, Postoperative nausea and vomiting, Cost-effectiveness

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Postoperative nausea and vomiting (PONV) is a common complication of surgery and anesthesia. PONV can result in physical and physiological complications, including aspiration of vomitus, esophageal trauma (Mallory-Weiss syndrome or Boerhaave's syndrome), dehydration, and alkalemia, as well as emotional distress.¹ Avoidance of PONV is a major concern for patients undergoing surgical anesthesia, more so than the issues of pain, dysphoria, decreased mental acuity, and extra cost of postoperative care.^{2,3}

The American Society of Health-System Pharmacists therapeutic guidelines on the pharmacologic management of nausea and vomiting recommends a 5-HT₃ receptor antagonist or droperidol for the prevention of PONV in adults and pediatric patients.⁴ Selective serotonin (5-HT₃) receptor antagonists, such as ondansetron, have become one of the most widely prescribed agents for the prevention of PONV. However, several studies suggest that antiemetics such as droperidol and prochlorperazine provide comparable or superior clinical efficacy.⁵⁻⁷ Cost analyses utilizing outpatient surgical settings indicate that the use of droperidol is also associated with greater cost-effectiveness.^{8,9} Chen et al. reported that prochlorperazine is clinically and statistically superior to ondansetron for the prevention of PONV after total hip replacement or total knee replacement procedures.

In 2001, the U.S. Food and Drug Administration added a "black box" warning indicating that droperidol may be associated with torsades de pointes; a coincidental shortage of intravenous prochlorperazine during the same year may have led to an increased use of 5-HT₃ receptor antagonists.¹⁰⁻¹³ Intravenous prochlorperazine has recently become available again, but at a higher average wholesale price (AWP): \$1.32, 2001 AWP versus \$9.56, 2004 AWP for 10 mg single-dose vial.¹⁴⁻¹⁶ An increase in price will obviously affect prochlorperazine's cost-effectiveness and may influence its use in the management of PONV.

A review of the literature failed to identify a comparison of the costs and benefits of ondansetron and prochlorperazine for the prevention of PONV. Therefore, we have utilized the previously published efficacy data conducted for ondansetron and prochlorperazine by Chen et al. to construct a cost-effectiveness analysis for the management of PONV in hospitalized patients using current costs. The main objective of this present study was to evaluate the cost-effectiveness of ondansetron and prochlorperazine in the prevention of PONV following total hip replacement or total knee replacement procedures.

Methods

Clinical data were derived from a previous study conducted in

TABLE 1 Demographic Characteristics of Patients Receiving Ondansetron and Prochlorperazine

Characteristic*	Ondansetron (n = 37)	Prochlorperazine (n = 41)	P Value
Mean age (years)	62.5	62.6	NS
Sex			
Female	24	25	NS
Male	13	16	NS
Surgical procedure			
Total hip replacement	19	21	NS
Total knee replacement	18	20	NS
Mean weight (kg)	87.7	88.2	NS
Smokers	4	6	NS
History of postoperative nausea and vomiting	15	11	NS
General anesthesia	26	26	NS
Regional anesthesia	28	36	NS
Mean duration of operation (hour)	3.3	3.2	NS
Mean duration of anesthesia (hour)	2.9	2.9	NS
Postoperative analgesia			
Epidural	25	33	NS
Patient-controlled analgesia	12	8	NS

* Clinical trial data from: Chen JJ, Frame DG, White TJ. Efficacy of ondansetron and prochlorperazine for the management of postoperative nausea and vomiting: a double-blind, comparative study. Arch Intern Med. 1998;158:2124-28.

NS=not statistically significant (P>0.10).

TABLE 2 Incidence of Nausea and Vomiting in Patients Treated With Ondansetron and Prochlorperazine*

Outcome	Ondansetron (n = 37)	Prochlorperazine (n = 41)	P Value	Relative Risk† (95% CI)
Nausea	30 (81.1%)	23 (56.1%)	0.02	1.45 (1.06-1.98)
Vomiting	18 (48.6%)	13 (31.7%)	0.13	1.53 (0.88-2.68)
PONV-free	7 (18.9%)	18 (43.9%)	0.02	0.43 (0.20-0.91)

* Clinical trial data from: Chen JJ, Frame DG, White TJ. Efficacy of ondansetron and prochlorperazine for the management of postoperative nausea and vomiting: a double-blind, comparative study. Arch Intern Med. 1998;158:2124-28.

† Risk of ondansetron relative to prochlorperazine.

CI=confidence interval; PONV=postoperative nausea and vomiting.

TABLE 3 Administration of Rescue Doses in Patients Treated With Ondansetron and Prochlorperazine*

Rescue Dose Administration	Ondansetron (n = 37)	Prochlorperazine (n = 41)	P Value	Relative Risk† (95% CI)
Patients receiving a rescue dose	17 (45.9%)	11 (26.8%)	0.08	1.71 (0.93-3.17)
Mean number of rescue doses‡ (SD)	2.06 (1.56)	1.73 (1.01)	0.71	N/A

* Clinical trial data from: Chen JJ, Frame DG, White TJ. Efficacy of ondansetron and prochlorperazine for the management of postoperative nausea and vomiting: a double-blind, comparative study. Arch Intern Med. 1998;158:2124-28.

† Risk of ondansetron relative to prochlorperazine.

‡ Among patients who received a rescue dose.

CI=confidence interval.

1995 and 1996 to evaluate the efficacy of ondansetron and prochlorperazine for the prevention of PONV.⁷ Patients were randomized in a double-blinded manner to receive either ondansetron (4 mg) administered intravenously or prochlorperazine (10 mg) administered intramuscularly for the prophylaxis of PONV. A simplified risk score was used to estimate the probability of PONV, based on the presence of the following risk factors: female sex, previous history of PONV or motion sickness, nonsmoking status, and anticipated use of postoperative opioids.¹⁷⁻¹⁹ The presence of 0, 1, 2, 3, or 4 of these risk factors correlate to incidences of PONV of 10%, 21%, 39%, 61%, and 79%, respectively.¹⁷

The initial antiemetic dose was administered to the patient immediately following surgery. A combination of nitrous oxide and isoflurane was used for inhalation anesthesia. Regional anesthesia consisted of either an epidural of bupivacaine or lidocaine. Intravenous fentanyl and midazolam were administered for induction of anesthesia. Patients received either intravenous morphine (i.e., patient controlled administration device) or fentanyl epidurally for postoperative analgesia, and supplemental doses were allowed only under the direction of the attending physician.

In the previous clinical study, the presence and severity of nausea or vomiting was assessed and documented at 14 predefined time intervals for a 48-hour period after surgical procedure. If vomiting occurred or if the patient requested, rescue antiemetic doses were provided, consisting of the originally assigned study drug (along with concomitant placebo). Rescue doses were administered every 4 hours as needed during the 48-hour observation period. An additional rescue dose was administered if symptoms of nausea and vomiting continued without relief after 1 hour. If nausea and vomiting persisted or progressed in severity, the patient was unblinded and treated at the discretion of the physician. Patients were not excluded from the evaluation of efficacy if unblinded.

The following definitions were adopted for the purposes of the previous study and this study as well: (1) nausea—a subjectively unpleasant sensation associated with awareness of the urge to vomit but not necessarily followed by retching or vomiting and (2) vomiting—the involuntary and forceful expulsion of gastric contents from the mouth.

Statistical Analysis

The chi-square test and Fisher's exact test were used for analyses of categorical outcomes. The 2-sample *t* test was used for analyses of all parametric data. The Mann-Whitney U test was used for analysis of continuous data that were nonparametric. All reported *P* values are 2-tailed. The level of significance was assumed to be *P* < 0.05. All statistical analyses were conducted with SAS Software (SAS Institute Inc, Cary, NC) and SPSS for Windows, Version 11.0.1 (SPSS Inc, Chicago, IL).

Cost-Effectiveness Analysis

The cost-effectiveness ratio (C/E ratio) is defined as the cost per

successfully treated patient (i.e., cost to keep one patient free of nausea and/or vomiting). We performed our cost-effectiveness analyses from a provider (i.e., hospital) perspective. Cost of therapy was calculated based on 2004 AWP of ondansetron (Zofran) 4 mg single-dose vials (\$26.71) and prochlorperazine 10 mg single-dose vials (\$9.56).¹⁶ Cost of supplies associated with drug administration (e.g., plastic syringes, saline flushes) were omitted since they were similar between the 2 groups. Also, because labor for drug preparation and administration can be absorbed to perform other routine activities, labor-associated costs were excluded.

Since the rate of clinical success from other institutions may differ from our results, we conducted a 1-way sensitivity analysis to account for variability in efficacy and to strengthen the external validity of our analysis. We reviewed 5 previous studies to determine how the success rate would be varied, which served as the basis of the sensitivity analysis.²⁰⁻²⁴ For our sensitivity analysis, we explored the effect of varying the rate of successfully treated patients (percentage of patients free of vomiting) and estimated the resulting total costs per patient. Another 1-way sensitivity analysis was performed to test the variability in costs of ondansetron. The cost of ondansetron was reduced up to 50% from AWP listings while keeping the efficacy rate constant, and the C/E ratios were reconstructed for each outcome.

Results

A total of 80 patients were enrolled in the original clinical study conducted during 1995 and 1996. However, 2 patients in the ondansetron group were excluded from data analysis on the basis of incomplete data collection, resulting in a sample size of 78 patients (62.8% female and 37.2% male). No significant adverse drug reactions were reported from either group. No statistically significant differences in baseline characteristics were found between the 2 groups (Table 1). All patients had at least 2 or more risk factors of PONV (e.g., female sex, previous history of PONV or motion sickness, nonsmoking status, and anticipated use of postoperative opioids), resulting in an estimated risk of PONV that exceeded 40% according to the simplified risk score.¹⁷ Of the 78 patients, 33.3% had 2 risk factors, 47.4% had 3 risk factors, and 19.2% had 4 risk factors. The proportion of patients who had at least 1 physical therapy session cancelled due to postoperative nausea or vomiting was similar between the ondansetron and prochlorperazine groups (10.8% and 7.3%, respectively; $P=0.70$). Additionally, the mean length of hospital stay was similar, 5.08 (1.44) days for the ondansetron group and 4.88 (1.19) days for the prochlorperazine group ($P=0.50$).

Patients who received ondansetron experienced nausea 1.45 times more often than patients who received prochlorperazine, and they were 1.53 times more likely to have at least 1 vomiting episode (Table 2). A greater proportion of ondansetron-treated patients required supplemental rescue doses compared with

TABLE 4 Cost-Effectiveness Analyses of Ondansetron and Prochlorperazine for the Management of Postoperative Nausea and Vomiting

Outcome	Cost per Patient* (\$)	Success Rate (Fraction in Each Group)	Cost-Effectiveness Ratio (\$)
Nausea-free			
Ondansetron	51.98	0.189	275.01
Prochlorperazine	13.99	0.439	31.87
Vomiting-free			
Ondansetron	51.98	0.514	101.13
Prochlorperazine	13.99	0.683	20.48
PONV-free			
Ondansetron	51.98	0.189	275.01
Prochlorperazine	13.99	0.439	31.87

* Includes cost of drugs (prophylactic dose and rescue doses). 2004 average wholesale prices: ondansetron (Zofran) 4 mg single-dose vial = \$26.71; prochlorperazine 10 mg single-dose vial (generic, Watson Pharmaceuticals) = \$9.56

PONV = postoperative nausea and vomiting.

FIGURE 1 Efficacy-Adjusted Sensitivity Analysis of Ondansetron Versus Prochlorperazine for the Prevention of Postoperative Vomiting*

*The rates of success varied from a lower limit of 35% and an upper limit of 75% based on previous efficacy studies.¹³⁻¹⁷

prochlorperazine-treated patients (Table 3) although this was determined to be not statistically significant ($P=0.08$).

The C/E ratios, based on different outcomes, are listed in Table 4. The mean total costs of PONV management per patient in the prochlorperazine and ondansetron groups were \$13.99 and \$51.98, respectively. For each circumstance, prochlorperazine had a lower C/E ratio than ondansetron. The cost per successfully treated patient was \$275.01 with ondansetron and \$31.87 with

TABLE 5 Cost-Adjusted Sensitivity Analysis of Ondansetron

Strategy	Cost per Patient* (\$)	Cost-Effectiveness Ratio (\$)		
		Nausea-Free	Vomiting-Free	PONV-Free
Success rate	—	0.189	0.514	0.189
0% reduction in ondansetron cost	51.98	275.01	101.13	275.01
25% reduction in ondansetron cost	38.98	206.27	75.85	206.27
50% reduction in ondansetron cost	25.99	137.51	50.56	137.51

* Includes cost of drugs (prophylactic and rescue doses); 25% and 50% reduction from average wholesale prices (AWP) for ondansetron (Zofran) 4 mg single-dose vial (2004 AWP = \$26.71).

PONV = postoperative nausea and vomiting.

prochlorperazine. Ondansetron was found to be more expensive and less efficacious, resulting in much higher C/E ratios compared with prochlorperazine.

After reviewing previous efficacy studies for the 1-way sensitivity analysis (Figure 1), the upper limit of success was determined to be approximately 75% and the lower limit of success to be 35%.²⁰⁻²⁴ The 1-way sensitivity analysis depicts the total cost of therapy for each antiemetic as the rate of success is independently varied from 35% to 75%. The results indicate that prochlorperazine is dominant over this range, making it more cost effective than ondansetron. The C/E ratios derived from the sensitivity-adjusted costs of ondansetron are listed in Table 5. Even with a 50% reduction in the cost of ondansetron, prochlorperazine is still superior to ondansetron.

Discussion

If a treatment is more effective and less costly than another, then the treatment is considered the dominant strategy. Our study indicates that the use of prochlorperazine for the prevention of inpatient PONV is a dominant strategy over the use of ondansetron. The results of our sensitivity analysis and cost-adjustment analysis strengthened the validity of our conclusion. The sensitivity analysis indicates that prochlorperazine is more cost effective even when efficacy and drug costs are varied, which bolsters support for the preferred use of prochlorperazine. The cost-effectiveness of prochlorperazine would have been even more favorable if we had used actual purchase prices for generic prochlorperazine, \$2.05 per 10 mg single-dose vial (medical center study site pharmacist, e-mail communication, March 11, 2005), 79% less than the AWP (\$9.56) used in our analyses.

Our results are consistent with a recent study by Hill and colleagues demonstrating that droperidol, another traditional antiemetic agent, is associated with greater effectiveness and lower costs when compared with ondansetron for the prophylaxis of PONV in an ambulatory surgical unit.⁹ However, the “black

box” warning in droperidol labeling of potential adverse cardiac conductance changes and QT prolongation potentially reduces the availability of effective low-cost alternatives to relatively expensive 5-HT₃ agents. In addition, there have been reports of QT prolongation associated with 5-HT₃ receptor antagonists, ondansetron and granisetron, and one clinical reference classifies these 2 drugs as a level-2 risk for torsades de pointes.²⁵ Although the incidence of adverse cardiac events with 5-HT₃ agents appears to be low, the use of prochlorperazine may be a safer and more cost-effective antiemetic for the prevention of PONV.

Limitations

There are several limitations to our analysis. First, it should be understood that this analysis was conducted specifically on data from a previously conducted clinical trial of 78 patients undergoing total hip replacement or total knee replacement procedures during approximately a 1-year period from 1995 to 1996. The sample size is also small. On the other hand, there are no other published data evaluating the economics of prochlorperazine in comparison with ondansetron for the prevention of PONV.

It is possible that the incidence of PONV may be different in other types of surgery; thus, our results can only be extrapolated to orthopedic surgical patients with hip or knee replacements. Although we measured differences in physical therapy cancellations, length of hospital stay, and costs of antiemetic drug per patient, we did not measure other PONV-related factors that may also affect total costs. For example, we did not measure direct costs of staff time and sanitizing materials associated with emesis clean up and disposal and intangible costs associated with patients’ preference for intravenous or intramuscular injections, satisfaction with antiemetic therapy, willingness to pay to avoid a PONV experience, and quality of life. Length of stay in the hospital was measured (the mean length of stay did not significantly differ between the ondansetron group and prochlorperazine group [5.1 days vs. 4.9 days, $P = 0.50$]) but was not included in the cost of therapy. It is uncertain whether or not PONV contributes to prolonged stays in the hospital and, therefore, incurs additional costs associated with therapy. Finally, costs of drug administration supplies (including syringes, saline flushes, etc.) were also not included in the calculation of cost of therapy since patients, on average, only received approximately 2 doses of each antiemetic. Therefore, the cost of drug administration supplies contributed minimally to the total cost.

Conclusion

The use of prochlorperazine is significantly more cost effective than ondansetron, even across a wide range of efficacy and drug costs, for the prevention of PONV in an adult inpatient population undergoing total hip replacement or total knee replacement procedures.

DISCLOSURES

No outside funding supported this study. Authors Peter Chang, Mark Okamoto, and Jack Chen disclose no potential bias or conflict of interest relating to this article; author David Frame discloses that he is a consultant to and participates in the speakers bureau of GlaxoSmithKline, Roche, and Aventis. Chang served as principal author of the study. Study concept and design were contributed by all authors. Analysis and interpretation of data and statistical expertise were contributed by Chang and Okamoto. Drafting of the manuscript was primarily the work of Chang and Chen, and its critical revision was the work of all authors.

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