

A Comparison of Ondansetron with Promethazine for Treating Postoperative Nausea and Vomiting in Patients Who Received Prophylaxis with Ondansetron: A Retrospective Database Analysis

Ashraf S. Habib, MBBCh, MSc,
FRCA

Johnatan Reuveni

Akiko Taguchi, MD, PhD

William D. White, MPH

Tong J. Gan, MB, FRCA,
FFARCS(I)

BACKGROUND: There are little data on the efficacy of antiemetics for treating postoperative nausea and vomiting (PONV) in patients who received prior PONV prophylaxis.

METHODS: In this retrospective database analysis, we compared the efficacy of ondansetron with that of promethazine for treating PONV in adults receiving general anesthesia who failed ondansetron prophylaxis.

RESULTS: Three thousand sixty-two patients received ondansetron and 752 received promethazine after failure of ondansetron prophylaxis. The complete response (no PONV and no further rescue) was 68% after administration of promethazine and 50% after ondansetron administration ($P < 0.0001$). There was no difference in complete response between 6.25 mg and higher doses of promethazine.

CONCLUSIONS: Promethazine was significantly more effective than ondansetron for treating PONV after failed ondansetron prophylaxis. Promethazine 6.25 mg was as effective as higher doses.

(Anesth Analg 2007;104:548–51)

There is a paucity of data on the treatment of established postoperative nausea and vomiting (PONV). Expert opinion recommends switching to an antiemetic from a different class in patients who develop PONV despite prophylaxis (1). There are, however, limited data to support this recommendation.

The serotonin receptor antagonists are widely used in the management of PONV. Their side-effect profile, and lack of sedation in particular, makes them particularly popular for ambulatory surgical patients. In patients who fail prophylaxis with ondansetron, a repeat dose of ondansetron was no more effective than placebo for the treatment of established PONV (2). A small pilot study suggested that promethazine and dimenhydrinate may be more effective for the treatment of established PONV than a repeat dose of ondansetron (3). However, no previous large studies have compared other antiemetics with ondansetron for the treatment of PONV in patients who received prior prophylaxis with ondansetron.

At our institution, ondansetron is the most commonly used drug for both the prophylaxis and treatment of PONV. In the postanesthesia care unit

(PACU), promethazine is the second most commonly used antiemetic. The primary aim of this retrospective database analysis was to compare the efficacy of a repeat dose of ondansetron versus promethazine for the treatment of established PONV in the PACU in patients who failed ondansetron prophylaxis. A secondary aim of this study was to compare the efficacy of different doses of promethazine when used for the rescue treatment of PONV in the PACU after failure of ondansetron prophylaxis.

METHODS

After IRB approval, we retrospectively retrieved data from the Duke Perioperative Anesthesia Database between April 2001 and June 2005. We searched for patients aged >18 yr who received general anesthesia for surgical procedures lasting 30–240 min. We identified patients who received inhaled drugs (isoflurane or sevoflurane with or without nitrous oxide) for maintenance of anesthesia and had PONV prophylaxis with ondansetron 4 mg. We included patients who received ondansetron or promethazine as the first rescue drug for the treatment of PONV in the PACU in whom the time from administration of prophylactic ondansetron to the time of the first rescue antiemetic in the PACU did not exceed 4 h. A complete response to the first rescue drug was defined as no further nausea, vomiting, or need for other antiemetics in the PACU.

Data on nausea and vomiting were recorded by PACU nurses during patients' PACU stay. Severity of

From the Department of Anesthesiology, Duke University Medical Center, Durham, North Carolina.

Accepted for publication October 16, 2006.

Address correspondence and reprint requests to Ashraf S. Habib, MBBCh, MSc, FRCA, Department of Anesthesiology, Box 3094, Duke University Medical Center, Durham, NC, 27710. Address e-mail to habib001@mc.duke.edu.

Copyright © 2007 International Anesthesia Research Society
DOI: 10.1213/01.ane.0000252433.73485.be

nausea was recorded as verbal rating score with “0” representing no nausea and “10” representing worst nausea. Sedation was assessed using the Ramsay score (4). We retrieved information about the first Ramsay score recorded on admission to the PACU, and the highest Ramsay score subsequently recorded during the patients’ PACU stay. We also retrieved information about the duration of PACU stay as well as opioid consumption in the operating room and PACU converted to morphine dose equivalents.

Descriptive statistics were used to summarize the demographic characteristics of patients. Data were analyzed with the *t*-test and the Wilcoxon’s ranked sum test for continuous data, and the χ^2 test for categorical data. To assess the change in sedation level in the promethazine group in the PACU, a change score was calculated as the highest Ramsay score recorded in the PACU minus the first score. Mantel-Haenszel χ^2 test was used to assess the change in sedation level. For subgroup analysis in patients who received rescue with promethazine, doses larger than 6.25 mg were combined. $P < 0.05$ was accepted as statistically significant.

RESULTS

A total of 23,812 patients received prophylaxis with ondansetron. Of those, 18,209 patients met the inclusion criteria and were included in the analysis. Rescue antiemetics were required in 4391 patients (31%). Of those, 3151 (72%) received ondansetron, and 759 (17%) received promethazine. The time from the administration of prophylactic ondansetron until the time of administration of the first rescue antiemetic was 4 h or less in 3062 patients who received rescue with ondansetron (ondansetron group) and in 752 patients who received rescue with promethazine (promethazine group). Patient demographics, types of surgery, and intraoperative opioids are presented in Table 1.

In the PACU (Table 2), the complete response rate was 68% after rescue with promethazine and 50% after rescue with a repeat dose of ondansetron ($P < 0.0001$). There was no difference between the two groups in the amount of opioid boluses given for the control of acute pain or in the duration of PACU stay. On admission to the PACU, 36% of patients in both groups had a first recorded Ramsay score >2 . However, significantly more patients in the promethazine group had a subsequently recorded Ramsay score >2 during PACU stay compared with the ondansetron group (45% vs 41%, $P = 0.04$).

The dose of ondansetron used in PACU was 4 mg in all patients. The dose of promethazine was 6.25 mg in 534 patients, 12.5 mg in 147 patients, and 25 mg in 71 patients. There was no significant difference in patients’ demographics, duration of surgery, and dose of intraoperative opioids among these promethazine doses. In the PACU, there was also no difference in the dose of

Table 1. Patient Demographics, Type and Duration of Surgery, and Use of Intraoperative Opioids

	Ondansetron group (n = 3062)	Promethazine group (n = 752)
Age (yr)	49 ± 17	44 ± 14*
Height (cm)	169 ± 12	167 ± 10
Weight (kg)	82 ± 22	82 ± 23
Females	1971 (64)	538 ± 72†
Type of surgery		
Gynecologic	538 (18)	246 (33)*
General	821 (27)	193 (26)
Orthopedic	605 (20)	95 (13)*
Plastic	211 (7)	54 (7)
Urosurgery	344 (11)	59 (8)‡
Other	282 (9)	21 (3)*
Duration of surgery (min)	113 (54)	112 (53)
Intraoperative opioids (morphine equivalents) (mg)	30 (18)	32 (19)

Values within parentheses indicate percentages.

* $P < 0.0001$, † $P = 0.0002$, ‡ $P = 0.065$.

Table 2. Postanesthesia Care Unit Data

	Ondansetron group (n = 3062)	Promethazine group (n = 752)
Vomiting before rescue	308 (10) ^a	57 (7.5)*
Nausea score within 15 min of rescue ^b	1 (0–10)	2 (0–10)
Complete Response to First Rescue Antiemetic	1538 ± 50	512 ± 68†
PACU opioid boluses (morphine equivalents) (mg)	11 ± 11	11 ± 10
First Ramsay score in PACU >2	1101 (36)	273 (36)
Worst Ramsay score in PACU >2	1251 (41)	338 (45)*
Duration of PACU stay (min)	174 ± 95	175 ± 81
Time from administration of first PACU antiemetic to PACU discharge	117 ± 95	116 ± 83

PACU = Postanesthesia care unit.

^a Values within parentheses indicate percentages.

^b Values are given as medians and ranges within parentheses.

* $P = 0.04$, † $P < 0.001$.

opioid boluses, duration of PACU stay, change in Ramsay score during PACU stay or complete response to the rescue antiemetic between the 6.25 mg and the higher doses of promethazine ($P = 0.3$) (Table 3).

DISCUSSION

In this retrospective database analysis, promethazine was significantly more effective than ondansetron for the treatment of established PONV in patients who

Table 3. Comparison Between 6.25 mg and >6.25 mg Doses of Promethazine

	Promethazine 6.25 mg (n = 534)	Promethazine >6.25 mg (n = 218)
Complete Response to First Rescue Antiemetic	358 (67) ^a	154 (71)
PACU opioid boluses (morphine equivalents) (mg)	11 ± 10	10 ± 10
First Ramsay score in PACU >2	210 (39)	63 (29)*
Worst Ramsay score in PACU >2	258 (48)	80 (37)†
Number of patients who had an increase in Ramsay score during PACU stay	101 (19)	37 (17)
Increase in Ramsay score during PACU stay compared to first recorded score ^b	0 (0–5)	0 (0–5)

PACU = postanesthesia care unit.

^a Values within parentheses indicate percentages.

^b Values are given as medians and ranges within parentheses.

* $P = 0.008$, † $P = 0.004$.

failed ondansetron prophylaxis. There was no difference in efficacy between 6.25 mg and higher doses of promethazine for the treatment of established PONV in those patients.

Our findings confirm previous data suggesting the limited efficacy of a repeat dose of ondansetron for the treatment of established PONV in the PACU (2,3). The package insert for ondansetron also specifically states that a second dose of ondansetron does not provide additional control if the first prophylactic dose has failed (5). This also agrees with expert opinion suggesting the use of an antiemetic from a different class for the treatment of established PONV in patients who failed prophylaxis (1).

Promethazine is an effective antiemetic with a long duration of action. Its use might be limited by its sedative side effects (6). Some studies however found no difference in sedation or duration of PACU stay after prophylaxis with ondansetron 4 mg or promethazine 12.5–25 mg. (7) It has been suggested that the sedative effect of promethazine might be dose dependent (8). In this study, the use of promethazine was associated with increased sedation compared with ondansetron. There was no difference in efficacy or sedation between 6.25 mg promethazine and higher doses. The similar efficacy of 6.25 mg promethazine to doses of 12.5 mg or higher, agrees with previous data demonstrating the lack of dose response of other antiemetics including serotonin receptor antagonists for the treatment of PONV (9).

This database analysis has its limitations. The data have been retrospectively collected. Although the database was specifically designed to collect PONV outcome variables, the quality of data entry is operator-dependant and might therefore suffer from inaccuracies and under-reporting, especially when new nurses are starting to use our electronic charting system. Specifically, though the PACU nurses are vigilant about recording the drugs given, the documentation of the occurrence of nausea and vomiting seemed to be under-reported and not complete as more patients received rescue compared with the reported incidence of PONV. Because antiemetics are given according to our PACU protocol only for

the treatment of established PONV, we believe that the administration of rescue drugs represents a surrogate end-point that more accurately represents the occurrence of PONV than the recorded incidence of these events. In fact, the incidence of rescue use in this study (31%) agrees with the reported incidence of PONV in randomized controlled trials (10,11).

Another limitation is that the choice of the rescue antiemetic was at the discretion of the attending anesthesiologist and was not randomized. It is important to note, however, that the choice of rescue antiemetics at our institution and the order in which they are given are determined by the attending anesthesiologist prior to the patient's admission to the PACU. The severity of PONV, therefore, does not affect the choice or the dose of the rescue antiemetic. Some data about the patients underlying risk for PONV, including history of PONV/motion sickness, and smoking status, were not documented, and therefore, we cannot determine if the two groups were comparable in terms of PONV risk. It is not known, however, whether the patients who are at higher risk for developing PONV are also more resistant to the treatment of established PONV. Furthermore, given the lack of data in this area and the difficulty in performing PONV rescue trials of sufficient power (9), we believe these data provide valuable information for the management of PONV in the PACU.

In conclusion, in patients who failed PONV prophylaxis with ondansetron, the use of promethazine was significantly more effective than a repeat dose of ondansetron for the treatment of established PONV in the PACU. Promethazine 6.25 mg IV was as effective as higher doses.

REFERENCES

1. Gan TJ, Meyer T, Apfel CC, et al. Consensus guidelines for managing postoperative nausea and vomiting. *Anesth Analg* 2003;97:62–71.
2. Kovac AL, O'Connor TA, Pearman MH, et al. Efficacy of repeat intravenous dosing of ondansetron in controlling postoperative nausea and vomiting: a randomized, double-blind, placebo-controlled multicenter trial. *J Clin Anesth* 1999;11:453–9.

3. Habib AS, Gan TJ. The effectiveness of rescue antiemetics after failure of prophylaxis with ondansetron or droperidol: a preliminary report. *J Clin Anesth* 2005;17:62–5.
4. Ramsay MA, Savege TM, Simpson BR, Goodwin R. Controlled sedation with alphaxalone-alphadolone. *BMJ* 1974;2:656–9.
5. Zofran (ondansetron hydrochloride) injection [package insert]. Research Triangle Park, NC: GlaxoSmithKline, 2004.
6. Rowbotham DJ. Current management of postoperative nausea and vomiting. *Br J Anaesth* 1992;69:465–595.
7. Khalil S, Philbrook L, Rabb M, et al. Ondansetron/promethazine combination or promethazine alone reduces nausea and vomiting after middle ear surgery. *J Clin Anesth* 1999;11:596–600.
8. Habib AS, Breen TW, Gan TJ. Promethazine adverse events after implementation of a medication shortage interchange [comment]. *Ann Pharmacother* 2005;39:1370.
9. Kazemi-Kjellberg F, Henzi I, Tramer MR. Treatment of established postoperative nausea and vomiting: a quantitative systematic review. *BMC Anesthesiol* 2001;1:2.
10. Fortney JT, Gan TJ, Graczyk S, et al. A comparison of the efficacy, safety, and patient satisfaction of ondansetron versus droperidol as antiemetics for elective outpatient surgical procedures. S3A-409 and S3A-410 Study Groups. *Anesth Analg* 1998;86:731–8.
11. Apfel CC, Korttila K, Abdalla M, et al. A factorial trial of six interventions for the prevention of postoperative nausea and vomiting. *N Engl J Med* 2004;350:2441–51.

ERRATUM

In the December 2006 issue, in Mencke et al.'s response to the Letter to the Editor by Tornero-Campello, "Rapid-Sequence Induction: Rocuronium or Suxamethonium?" (*Anesth Analg* 2006;103:1579), the author's name in Reference 1 was incorrect. The correct Reference 1 should be:

1. Tornero-Campello G. Rapid-sequence induction: rocuronium or suxamethonium? *Anesth Analg* 2007;103:1579.

The publisher apologizes for the error.