

Prophylactic Antiemetics for Laparoscopic Cholecystectomy: Ondansetron Versus Droperidol Plus Metoclopramide

Richard A. Steinbrook, MD, Dubravka Freiberger, MD, James L. Gosnell, RN, and David C. Brooks, MD

Departments of Anesthesia and Surgery, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts

Two hundred adults undergoing laparoscopic cholecystectomy were enrolled in a prospectively randomized, double-blind investigation comparing ondansetron, 4 mg (Group O) with the combination of droperidol, 0.625 mg, and metoclopramide, 10 mg (Group DM). Antiemetic drugs were administered intravenously (IV) after induction of general anesthesia (propofol, desflurane). Moderate or severe nausea in the postanesthesia care unit was treated with the crossover drug, i.e., ondansetron for patients in Group DM or droperidol plus metoclopramide for patients in Group O. Data were analyzed using *t*-tests and χ^2 analyses, with *P* < 0.05 considered statistically significant. The groups were similar with respect to gender, age,

weight, duration of surgery, number receiving intraoperative atropine or ephedrine, number admitted overnight, and time to discharge home. Of 102 patients in Group O, 44 required antiemetics in the postanesthesia care unit, compared with 24 of 98 patients in Group DM (*P* < 0.01). One patient (in Group DM) was admitted for persistent nausea. In conclusion, droperidol 0.625 mg IV in combination with metoclopramide 10 mg IV was more effective in preventing postoperative nausea than was ondansetron 4 mg IV in patients undergoing laparoscopic cholecystectomy, with no difference in the time to discharge.

(Anesth Analg 1996;83:1081-3)

Postoperative nausea and vomiting (PONV) are unpleasant for the patient and may delay discharge from the ambulatory surgery unit or result in unexpected overnight hospitalization after laparoscopic cholecystectomy. Ondansetron, a selective serotonin subtype 3 (5-HT₃) antagonist, is the first of a new class of antiemetic drugs recently introduced into practice. This study compared the efficacy of ondansetron with that of a commonly used combination of older antiemetics, droperidol and metoclopramide, in preventing nausea after laparoscopic cholecystectomy. Since patients may become sedated after droperidol and metoclopramide, to keep the investigation double-blind, antiemetic drugs were administered after induction of general anesthesia.

Methods

With approval of the hospital's Human Subjects Committee and written, informed consent, 215 patients scheduled for laparoscopic cholecystectomy were enrolled in a randomized, double-blind cross-over

study. Patients were sedated preoperatively with intravenous (IV) midazolam (1-2 mg) and fentanyl (50-100 μ g). General anesthesia was induced with propofol (1.5-2.5 mg/kg) and vecuronium (0.1 mg/kg). Immediately after tracheal intubation, patients received two 2-mL IV injections, either droperidol 0.625 mg plus metoclopramide 10 mg (Group DM) or ondansetron 4 mg plus saline (Group O). Antiemetic drug preparation and randomization were performed by an unblinded research pharmacist, using a computer program to assign patient treatment blocks of four from a published table of random numbers (1); physicians and patients were blinded to the identity of antiemetics. Anesthesia was maintained with desflurane-air-oxygen and additional fentanyl and vecuronium. Intraoperative bradycardia (heart rate < 50 bpm) or hypotension (systolic blood pressure < 90 mm Hg) were treated with atropine, 0.4 mg IV, or ephedrine, 5-10 mg IV, respectively, at the discretion of the anesthesiologist. Ketorolac 30 mg IV was administered during skin closure. Neuromuscular block was reversed with glycopyrrolate (0.6-1.0 mg) and neostigmine (3.0-5.0 mg) IV prior to extubation of the trachea. Postoperative pain was treated with IV fentanyl or morphine, as needed. Moderate or severe nausea or vomiting in the postanesthesia care unit

Accepted for publication July 5, 1996.

Address correspondence and reprint requests to Richard A. Steinbrook, MD, Department of Anesthesia, Brigham and Women's Hospital, 75 Francis St., Boston, MA 02115.

Table 1. Patient Data

	Group O (ondansetron)	Group DM (droperidol plus metoclopramide)
<i>n</i> (M/F)	102 (12/90)	98 (16/82)
Age (yr)	43 ± 13	44 ± 14
Weight (kg)	78 ± 21	77 ± 21
Surgery time (min)	75 ± 28	80 ± 33
Intraoperative fentanyl (μg)	244 ± 84	242 ± 94
Intraoperative atropine (<i>n</i>)	5	4
Intraoperative ephedrine (<i>n</i>)	14	20
Rescue antiemetic (<i>n</i>)	44	24*
Narcotic in postanesthesia care unit (<i>n</i>)	87	73
Admitted overnight (<i>n</i>)	54	50
Discharge time (min) (same day only)	293 ± 118	288 ± 99

Values are numbers of patients or means ± SD.
* *P* = 0.005.

(PACU) was treated with previously prepared cross-over drugs, i.e., ondansetron plus saline for patients in Group DM or droperidol plus metoclopramide for patients in Group O. Patients, investigators, and PACU nurses were all blinded to the identity of the intraoperative and cross-over antiemetics. Data were analyzed using *t*-tests and χ^2 analyses, with *P* < 0.05 considered statistically significant.

Results

Fifteen patients required conversion to open cholecystectomy and therefore were eliminated from the study; thus, 200 patients completed the protocol and are included in the following analysis. The groups were similar with respect to gender, age, weight, duration of surgery, intraoperative fentanyl dose, number receiving intraoperative atropine or ephedrine, number admitted to hospital overnight, and time to discharge home (for patients not admitted overnight) (Table 1). Of the 102 patients in Group O, 44 required antiemetic treatment in the PACU, compared with 24 of the 98 patients in Group DM (*P* < 0.01). Pain medication was requested by 87 patients in Group O vs 73 patients in Group DM (*P* = 0.06). Of patients admitted overnight, only one (in Group DM) was admitted specifically for persistent PONV.

Discussion

Nausea and vomiting are a significant problem in the postoperative period (2). Despite receiving propofol, which has been shown to have significant antiemetic properties (3,4), as well as either ondansetron or droperidol plus metoclopramide, 34% of the patients in the present study had moderate or severe nausea in the PACU, although only one patient was admitted to the hospital solely for persistent nausea.

While ondansetron may represent "a major advance in the management of chemotherapy-induced emesis" (5), its role in the prevention of PONV is less well established. In pediatric surgery, most published studies have found ondansetron to be more effective than placebo (6-10), droperidol (6,9), or metoclopramide (6,7) in preventing PONV, although one study found no difference between ondansetron and droperidol in emesis or time to discharge after pediatric strabismus repair (11). In adult gynecologic surgery, Leeser and Lip (12), Kenny et al. (13), and McKenzie et al. (14) found ondansetron to be superior to placebo in preventing PONV. In comparison with other antiemetics, though, the efficacy of ondansetron in gynecologic surgery is less clear: Grond et al. (15) found droperidol (2.5 mg IV) to be better than ondansetron (8 mg IV) in preventing PONV, although droperidol-treated patients were slower to recover from anesthesia, while Desilva et al. (16) found ondansetron not as effective as droperidol or perphenazine in preventing PONV in women undergoing abdominal hysterectomy. In one small study of ambulatory adults, ondansetron was no better than placebo (17).

There are no published studies comparing ondansetron with the combination of metoclopramide and droperidol. In pediatric strabismus surgery, Kymer et al. (18) found this combination (metoclopramide and droperidol) to be highly effective compared with placebo or either droperidol or metoclopramide alone. In a recent study of multimodal analgesia for ambulatory laparoscopic cholecystectomy, Michaloliakou et al. (19) used both metoclopramide and droperidol in all patients.

The difference in cost of the antiemetic drugs used in this study is substantial. The current (April 1996) pharmacy acquisition cost for a 4-mg vial of ondansetron is \$15.95, while a 5-mg vial of droperidol is \$0.37 and a 10-mg vial of metoclopramide is \$0.27. Pharmacy charges for these drugs are several times the acquisition costs.

Although we cannot exclude the possibility that a larger dose of ondansetron could have been more effective in preventing PONV in our patient population, a single 4-mg IV dose of ondansetron was highly effective in women undergoing ambulatory gynecology surgery in the study of McKenzie et al. (14). In pediatric patients, Watcha et al. (10) found 50 μg/kg

IV ondansetron (a dose comparable to ours) to be as effective as 100 $\mu\text{g}/\text{kg}$.

The decision to admit patients to a hospital overnight after laparoscopic cholecystectomy was at the discretion of the surgeon. The decision was usually based on nonmedical concerns, e.g., insurance reimbursement or home support systems. One patient (in Group DM) who had expected to go home on the day of surgery was admitted for persistent PONV; with bed rest and intravenous hydration, she recovered fully and was discharged the next day.

In conclusion, droperidol 0.625 mg IV in combination with metoclopramide 10 mg IV was more effective in preventing PONV than was ondansetron 4 mg IV in patients undergoing laparoscopic cholecystectomy. There were no differences in the numbers of patients admitted to the hospital or in time to discharge.

We are indebted to Robert O. Manning, GlaxoWellcome, Inc., for providing ondansetron; to Kathleen Benfell, RPh, and the Investigational Drug Service of the Brigham and Women's Hospital for preparing the drugs used in this study; and to Mary Aebischer for secretarial support.

References

1. Diem K, Lentner C, eds. *Documenta Geigy, scientific tables*. 7th ed. Basel, Switzerland: Ciba-Geigy, 1970:131.
2. Kapur PA. The big "little problem" [editorial]. *Anesth Analg* 1991;73:243-5.
3. Borgeat A, Wilder-Smith OHG, Saiah M, Rifat K. Subhypnotic doses of propofol possess direct antiemetic properties. *Anesth Analg* 1992;74:539-41.
4. Hvarfner A, Hammas B, Thörn S-E, Wattwil M. The influence of propofol on vomiting induced by apomorphine. *Anesth Analg* 1995;80:967-9.
5. Watcha MF, White PF. Postoperative nausea and vomiting: its etiology, treatment and prevention. *Anesthesiology* 1992;77:162-84.
6. Furst SR, Rodarte A. Prophylactic antiemetic treatment with ondansetron in children undergoing tonsillectomy. *Anesthesiology* 1994;81:799-803.
7. Rose JB, Martin TM, Corddry DH, et al. Ondansetron reduces the incidence and severity of poststrabismus repair vomiting in children. *Anesth Analg* 1994;79:486-9.
8. Ummenhofer W, Frei FJ, Urwyler A, et al. Effects of ondansetron in the prevention of postoperative nausea and vomiting in children. *Anesthesiology* 1994;81:804-10.
9. Davis PJ, McGowan FX Jr, Landsman I, Maloney K. 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. *Anesthesiology* 1995;83:956-60.
10. 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.
11. Litman RS, Wu CL, Lee A, et al. Prevention of emesis after strabismus repair in children: a prospective, double-blinded, randomized comparison of droperidol versus ondansetron. *J Clin Anesth* 1995;7:58-62.
12. Leeser J, Lip H. Prevention of postoperative nausea and vomiting using ondansetron, a new, selective, 5-HT₃ receptor antagonist. *Anesth Analg* 1991;72:751-5.
13. Kenny GNC, Oates JDL, Leeser J, et al. Efficacy of orally administered ondansetron in the prevention of postoperative nausea and vomiting: a dose ranging study. *Br J Anaesth* 1992;68:466-70.
14. McKenzie R, Kovac A, O'Connor T, et al. Comparison of ondansetron versus placebo to prevent postoperative nausea and vomiting in women undergoing ambulatory gynecologic surgery. *Anesthesiology* 1993;78:21-8.
15. Grond S, Lynch J, Diefenbach C, et al. Comparison of ondansetron and droperidol in the prevention of nausea and vomiting after inpatient minor gynecologic surgery. *Anesth Analg* 1995;81:603-7.
16. Desilva PHDP, Darvish AH, McDonald SM, et al. The efficacy of prophylactic ondansetron, droperidol, perphenazine, and metoclopramide in prevention of nausea and vomiting after major gynecologic surgery. *Anesth Analg* 1995;81:139-43.
17. Campbell C, Miller DD. Failure of ondansetron to control postoperative nausea and vomiting in ambulatory surgical patients. *Am J of Anesth* 1995;22:81-6.
18. Kymer PJ, Brown RE Jr, Lawhorn CD, et al. The effects of oral droperidol versus oral metoclopramide versus both oral droperidol and metoclopramide on postoperative vomiting when used as a premedicant for strabismus surgery. *J Clin Anesth* 1995;7:35-9.
19. Michaloliakou C, Chung F, Sharma S. Preoperative multimodal analgesia facilitates recovery after ambulatory laparoscopic cholecystectomy. *Anesth Analg* 1996;82:44-51.