

Bon Secours Richmond  
Pharmacy and Therapeutics Committees  
Ondansetron Oral Disintegrating Tablets  
11/2002

**Recommendation: MEC approved MRMC, RCH**

- Ondansetron 4-mg oral tablets (disintegrating & regular) are recommended for use in place of injectable ondansetron 4 mg for nausea and vomiting. The oral disintegrating table rapidly disintegrates on the tongue and does not require water to aid dissolution or swallowing.
- When ondansetron 4-mg injection is ordered an order for 4-mg oral disintegrating ondansetron tablet or regular tablet will also be entered. An additional message "Use oral Zofran in place of injectable Zofran except in cases where vomiting is contraindicated or when the patient is complaining of nausea and vomiting is imminent."
- Nursing staff will be educated to use the oral disintegrating tablets preferentially except in cases where vomiting is contraindicated or when the patient is complaining of nausea and vomiting is imminent.
- Ondansetron oral disintegrating tablets are not recommended to be given preoperatively to prevent postoperative nausea and vomiting as the FDA approved dosage, 16-mg, is much higher than injectable doses commonly used and is much more expensive. Ondansetron 4-8 mg injection is recommended to be given just before the end of surgery when postoperative nausea and vomiting must be avoided.
- In patients who do not achieve adequate control of postoperative nausea and vomiting following a single, prophylactic dose, administration of a second IV dose does not provide additional control of nausea and vomiting and is not recommended.
- When patients do not respond to initial therapy with an antiemetic agent, it is recommended that an agent from another pharmacologic class be use.
- A revision of the patient graphic record [NSG-047 (7/01)] is recommended to allow documentation of nausea and vomiting using a visual analog scale or a 10-point scale and actual number of emeses per shift.
- Opioid associated nausea and vomiting in chronic pain/cancer patients can be managed with antiemetics chosen according to their modes of actions. Metoclopramide is helpful when neuroleptics such as prochlorperazine, chlorpromazine, or haloperidol fail to control nausea and vomiting. Scopolamine or hydroxyzine may ameliorate symptoms as a result of their effects on the vestibular system. When patients complain of nausea and vomiting after opioid administration has begun, it is often helpful to administer an oral antiemetic on a fixed schedule for several days, after which as-needed dosing is usually adequate.

**Findings:**

- It is uncertain whether ondansetron's antiemetic action is mediated centrally, peripherally, or in both sites.
- Cytotoxic chemotherapy appears to be associated with release of serotonin from the enterochromaffin cells of the small intestine.
- Oral ondansetron 24-mg once a day, 8-mg twice a day, and 32-mg once a day were compared in 357 adult cancer patients receiving chemotherapy regimens containing a cisplatin dose  $\geq 50$  mg/m<sup>2</sup>. A total of 66% of patients in the ondansetron 24-mg once a day, 55% in the ondansetron 8-mg twice a day, and 55% in the ondansetron 32-mg once a day groups completed the 24 hour study period with no emetic episodes and no rescue antiemetic medications. Fifty six percent of patients receiving oral ondansetron 24-mg once a day experienced no nausea during the 24 hours study period, compared with 36% of patients in the oral ondansetron 8-mg twice a day group and 50% in the oral ondansetron 32-mg once a day group.

**Postoperative Nausea and Vomiting**

- Postoperative nausea and vomiting is influenced by the surgical procedure, the age and sex of the patient, and other medications administered. The overall frequency, defined by large-scale clinical trials is estimated to be 20-30%.
- Ondansetron 4-mg injection provides higher patient satisfaction than 10-mg of metoclopramide injection and freedom from nausea, but the incidence of vomiting is the same.
- Ondansetron 4-mg injection provides equivalent efficacy to 0.625 mg of droperidol injection for PONV.
- Ondansetron demonstrates greater antiemetic than antinausea efficacy.
- Patients who experience PONV after receiving prophylactic ondansetron (4 mg intravenous) prior to surgery were not responsive to additional doses of ondansetron (4 mg, IV) or another 5-HT<sub>3</sub> receptor antagonist.
- The combination of droperidol and ondansetron is more effective than either agent alone, and reduces the incidence of postoperative nausea and vomiting by 50% more than ondansetron alone.
- Droperidol doses range from 5-20 mcg/kg for procedures associated with moderately high frequency of emesis to 2.5-5 mg in adults and 50-75 mcg/kg in children in emetogenic procedures such as surgery for strabismus.
- The optimal dose of ondansetron injection to prevent postoperative nausea and vomiting appears to be 8 mg injection given at the end of surgery or 16 mg or oral ondansetron given preoperatively.
- The number needed to treat to prevent 1 case of POV is 5-6 patients.
- Oral disintegrating tablets have the same bioequivalence as oral tablets and solution.
- Ondansetron is approximately 56% bioavailable and displays non-linear absorption kinetics with 24% greater AUC with the 16-mg tablet as compared to the expected AUC from an 8-mg tablet dose.
- 26,648 doses of Zofran 4-mg injection were purchased in 2001 for a total cost of \$426,643.
- Thirty seven percent (37%) more oral doses (10,069) would be required to offset the potential cost saving of using oral Zofran in place of injectable.

- The FDA approved dosage of oral ondansetron disintegrating tablets for preoperatively prophylaxis to prevent postoperative nausea is 16-mg, which costs \$38.72 per dose versus \$16.01 for the FDA approved 4-mg injection dose.

<b>Cost Comparison of 4 mg Oral Versus IV Ondansetron</b>		
	Cost per dose	Cost for 26,648 doses (1 years usage)
Zofran 4 mg Injection	\$16.01	\$426,653
Zofran 4 mg Oral Disintegrating & Regular Tablets	\$11.62	\$309,656
<b>Potential Yearly Cost Savings</b>		<b>\$116,996</b>

<b>Antiemetics for Management of Postoperative Nausea and Vomiting in Adults</b>		
<b>Drug</b>	<b>Dosage and Timing of Administration</b>	<b>Cost Per Dose</b>
<b>Prophylaxis</b>		
Droperidol	0.625-1.25 mg IV before termination of anesthesia	\$0.88
Ondansetron	4 mg IV before termination of anesthesia	\$16.01
Metoclopramide	10 mg IV before termination of anesthesia	\$0.68
Promethazine	12.5-25 mg IV before induction of anesthesia	\$1.25
Prochlorperazine	5-10 mg IV 15-30 minutes before induction of anesthesia, may repeat once as needed	\$2.59
<b>Treatment</b>		
Droperidol	0.625-1.25 mg IV q3-4 hours prn	\$0.88
Ondansetron	4 mg IV	\$16.01
Metoclopramide	10 mg IV q4-6 hours prn	\$0.68
Promethazine	12.5-25 mg IM/IV q4 hours prn	\$1.25
Prochlorperazine	2.5-10 mg IM/IV q3-4 hours prn (maximum 40 mg per day)	\$2.59

### (1) LAPAROSCOPIC SURGERY

- (a) Combination DROPERIDOL-ONDANSETRON therapy was more effective in reducing postoperative nausea and vomiting (PONV) than monotherapy with either single agent in outpatients undergoing gynecological laparoscopy, based on a double-blind, randomized study (n=160) (Wu et al, 2000). Incidence of PONV in the first 24 hours following surgery (performed under general anesthesia) was 71% in the placebo group, 61% with droperidol alone (p=0.334 versus placebo), 46% with ondansetron alone (p=0.027 vs placebo), and 23% in the combination group (p less than 0.001 vs placebo). Comparative data showed that combination treatment was significantly superior to either droperidol alone (p less than 0.001) or ondansetron alone (p=0.036). The combination group had the lowest rate of requests for rescue medication. Doses were droperidol 1.25 milligrams (mg) and ondansetron 4 mg, both intravenously (Wu et al, 2000).
- (b) A 2-dose antiemetic regimen of droperidol or ondansetron and droperidol combined was not superior to single dose treatments in reducing postoperative (post-op) nausea and vomiting in women undergoing gynecologic laparoscopy. One hundred and six ASA Class I or II females were randomly assigned to 1 of 4 treatment groups: droperidol 1.25 milligrams (mg) followed by saline placebo (n=27); 2 doses of droperidol 1.25 mg (n=27); droperidol 1.25 mg plus ondansetron 4 mg followed by placebo (n=26); or 2 doses of combined droperidol 1.25 mg and ondansetron 4 mg (n=26). The first dose for each treatment was administered intravenously (IV) at anesthesia induction, and the second was infused 4 hours later. The overall incidence of post-op nausea and vomiting was 41%, 52%, 27%, and 38%, respectively. Rebound post-op nausea and vomiting, occurring at least 3.5 hours post-op, was also similar in frequency at 33%, 15%, 12%, and 19%, respectively. Verbal analog scores assessing patients' perceptions of post-op nausea and vomiting severity favored the combination groups during the rebound period (Warrick, 1999).
- (c) In a prospective, randomized, double-blind study, the combination of ondansetron and dexamethasone was more effective than ondansetron alone in preventing postoperative (post-op) nausea and vomiting following diagnostic laparoscopy. Fifty-one ASA I females (mean age 29 years) were assigned to receive either ondansetron 4 milligrams (mg) intravenously (IV) (Group 1, n=26) or ondansetron 4 mg plus dexamethasone 8 mg IV (Group 2, n=25) following anesthesia induction and tracheal intubation. Post-op nausea scores were numerically lower in Group 2 patients throughout the 24-hour monitoring period. The overall incidence of vomiting was greater in Group 1 (35%) versus Group 2 (8%) patients (p less than 0.05), reflecting a significant difference during the late, but not early, post-op period. The average time to discharge readiness was similar between groups (Rajeeva, 1999).

## **(2) MAJOR GYNECOLOGIC SURGERY**

- (a) The combination of ondansetron (4 milligrams (mg) at induction) and droperidol (2.5 mg at induction and 1.25 mg 12 hours later) was more effective than either agent alone or placebo in reducing postoperative nausea and vomiting. Women scheduled for intra- abdominal surgery (75% gynecological, 20% gastrointestinal, and 5% urological) were randomized to placebo (group 1; n=25), droperidol (group 2; n=25), ondansetron (group 3; n=25) or droperidol combined with ondansetron (group 4; n=25). Complete response occurred in 28% of patients in group 1, 60% in group 2, 56% in group 3, and 92% in group 4. Droperidol or ondansetron alone was more effective than placebo (p less than 0.05), but the combination was more effective than either drug alone (p less than 0.05). Patients who were randomized to droperidol treatment (group 2 and 4) experienced more sedation (p less than 0.05) than the placebo or ondansetron groups. A combination of ondansetron and droperidol may be useful in patients who are at high risk for PONV (eg, intra-abdominal surgery) (Pueyo et al, 1996).
- (b) Ondansetron with dexamethasone resulted in no episodes of postoperative nausea or vomiting in 84% of women undergoing major gynecologic surgery compared to 20% of women receiving placebo. One hundred women were randomly assigned to receive placebo, ondansetron 8 milligrams, dexamethasone 4 milligrams, or the combination of ondansetron with dexamethasone. All treatments were significantly better than placebo (p less than 0.05), and the combination was significantly better than either treatment alone (p less than 0.05). The most common adverse effect was headache and perineal itching in the dexamethasone group during administration (Lopez-Olaondo et al, 1996).

## **(3) STRABISMUS SURGERY**

- (a) Combination DROPERIDOL and ONDANSETRON, both given intravenously (IV), reduced the incidence of 24-hour postoperative nausea and vomiting (PONV) to a significantly greater extent than placebo or either drug alone, based on a double-blind prospective trial in pediatric patients undergoing elective STRABISMUS SURGERY (n=240; aged 1 to 15 years). Enrolled children were randomized to 4 groups including: Group DP-droperidol 25 micrograms/kilogram (mcg/kg) IV given after induction of anesthesia with normal saline given at the end of the procedure; Group OP-ondansetron 150 mcg/kg IV after induction and saline given at the end of the procedure; Group PP-normal saline placebo IV after induction and at the end of the procedure; and Group DO-droperidol 15 mcg/kg IV given after induction and ondansetron 100 mcg/kg IV given after the procedure. Each group included 60 children. The incidence of PONV was 13% in the combination group compared with 32% in the droperidol group (p less than 0.01), 37% in the ondansetron group (p less than 0.001); and 62.5% in the placebo group (p less than 0.001). Severe vomiting (defined as 3 or more episodes of vomiting) occurred in none of the combination-treated children, in 2 droperidol-treated children, in 4 ondansetron-treated children, and in 19 placebo-treated children (p less than 0.001, placebo versus combination; p less than 0.01 placebo versus droperidol or ondansetron). All subjects received standardized anesthetic technique, and postoperative ibuprofen 10 milligrams (mg)/kg orally if required (intramuscular diclofenac 0.5 mg/kg was given in those not tolerating oral intake) (Shende et al, 2001).