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Prophylactic oral dolasetron mesylate reduces nausea and vomiting after abdominal hysterectomy

Purpose: The incidence of postoperative nausea and vomiting (PONV) varies from 50% to 75% after gynaecological surgery under general anaesthesia. This study evaluates the dose-response relationships, safety, and efficacy of the new 5-HT_3 antagonist, dolasetron mesylate, in the prevention of PONV in women undergoing total abdominal hysterectomy (TAH).

Methods: Three hundred and seventy four women scheduled for TAH under general anaesthesia were studied at 13 Canadian centres. Patients received in a randomized, double-blind manner 25, 50, 100, or 200 mg dolasetron or placebo *po* one to two hours before induction of anaesthesia. The anesthetic protocol was standardized. Efficacy was evaluated for 24 hr after surgery by comparing the number of emetic episodes, administration of rescue medication, severity of nausea, and patient satisfaction.

Results: Analysis of complete response (no emetic episodes and no rescue for 24 hr) revealed a linear dose-response relationship across dolasetron groups ($P < 0.002$). Dolasetron 100 mg ($P < 0.003$) and 200 mg ($P < 0.01$) were superior to placebo. The percentage of patients with no emetic episodes increased from 29.3% (placebo) to 54.1% (100 mg). Subgroup analysis revealed ASA status (I>II), previous history of PONV, previous history of motion sickness, and total morphine dose (>55 mg associated with less PONV than < 55 mg) influenced the incidence of emetic symptoms, but did not alter the results of the primary analysis.

Conclusion: Prophylactic dolasetron (100 mg and 200 mg) reduces the incidence of PONV in patients having total abdominal hysterectomy.

Objectif : Après une intervention gynécologique sous anesthésie générale, l'incidence des nausées et des vomissements postopératoires (NVPO) varie de 50% à 75%. Cette étude évalue la relation dose-effet, la sécurité et l'efficacité d'un nouvel antagoniste 5-HT_3, le mésylate de dolasetron, lorsque administré pour prévenir les NVPO chez des femmes soumises à une hystérectomie abdominale totale (HAT).

Méthodes : Trois cent soixante-quatorze femmes programmées pour une HAT sous anesthésie générale ont participé à l'étude dans 13 centres canadiens. Les patientes ont reçu en double aveugle et aléatoirement 25, 50, 100 et 200 mg de dolasetron ou un placebo *po* une ou deux heures avant l'induction de l'anesthésie selon un protocole standard. L'efficacité a été évaluée pendant 24 h après la chirurgie en comparant le nombre d'épisodes émétiques, l'administration d'un médicament de sauvetage, la gravité des nausées et le degré de satisfaction.

Résultats : L'analyse de l'effet maximal (absence d'épisodes émétiques et abstention de médicament de sauvetage pendant 24 h) a révélé une relation dose-effet linéaire pour les groupes dolasetron ($P < 0,002$). Le dolasetron aux doses de 100 mg ($P < 0,003$) et de 200 mg ($P < 0,01$) était supérieur au placebo. Le pourcentage des patientes sans épisode émétique augmentait de 29,3% (placebo) à 54,1% (100 mg). Une analyse de sous-groupe montrait que l'état physique ASA (I < II), les antécédents de NVPO et du mal des transports, et la dose totale de morphine (> 55 mg associée à moins de NVPO que < 55 mg) influençaient l'incidence des symptômes émétiques mais ne changeaient pas les résultats de l'analyse principale.

Conclusion : La prophylaxie au dolasetron (100 mg et 200 mg) diminue l'incidence des NVPO chez les opérées pour hystérectomie abdominale totale.

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Accepted for publication July 26, 1997.

THE frequency of postoperative nausea and vomiting (PONV) in patients undergoing gynaecological surgery is between 50% and 75%.[1–4] Volunteers questioned about their concerns with surgery place PONV high on their lists surrounding anaesthesia and surgery and may accept other unpleasant side effects in an effort to avoid it.[5] Post-operative nausea and vomiting may prevent outpatients from returning home on their day of surgery or prolong the length of stay for inpatients post-surgery.[6] Patients may have nausea and vomiting that persists for days after surgery which delays return to normal daily activity[7] with potential cost effects upon the individual and society. Although rarely associated with serious morbidity, PONV has been described as the "big little problem"[8] because its presence suggests an unsatisfactory outcome to the surgeon, anaesthetist, and patient.

Dolasetron mesylate (MDL 73,147EF) and its major metabolite (MDL 74,156) are selective and potent 5-HT_3 receptor antagonists both *in vitro* and *in vivo*. Dolasetron mesylate exists in both salt and base preparations. In this study the salt was used (equivalent dolasetron base doses can be calculated using a conversion factor of 0.74). Dolasetron reduces nausea and vomiting associated with cancer chemotherapy[9–12] and radiotherapy.[13,14] Phase I and Phase II studies have revealed a low incidence of side effects, headache and diarrhea being the most frequently reported.[15,16]

This prospective, randomized, double-blind, placebo-controlled study examined the effectiveness and safety of oral dolasetron mesylate salt (25, 50, 100, and 200 mg) in the prevention of PONV in women undergoing total abdominal hysterectomy (TAH) under general anaesthesia. Three important variables influencing the incidence of PONV were standardized in this study: type of surgery, sex, and anaesthetic regimen.

The objectives of this study were to determine: 1) whether oral dolasetron given prior to anaesthesia and surgery reduced the incidence of PONV; 2) the most effective dose of dolasetron for reducing PONV; 3) the incidence and nature of dolasetron side effects; 4) other variables affecting the effectiveness of the drug.

Methods

Institutional ethics committee approval for the study was obtained at each site. After written informed consent, 374 non-pregnant, ASA I or II women between the ages of 18 and 70 yr booked for total abdominal hysterectomy (TAH) under general anaesthesia were enrolled at 13 Canadian centres. Medical history, demographic information (height, weight, age, ethnic origin), date of last menstrual cycle, history of previous PONV, and history of previous motion sickness were obtained before the study. A complete physical examination was performed. Blood samples for clinical laboratory evaluation were collected (CBC, electrolytes, BUN, creatinine, Ca^{++}, phosphorus, alkaline phosphatase, LDH, SGOT, SGPT, total bilirubin, uric acid, glucose, PT, PTT, INR), and a baseline ECG was done at the screening visit. Patients with a previous or current history of serious cardiovascular, respiratory, metabolic, hepatic, or renal dysfunction were excluded from the study as were patients who had used medication known to have potential antiemetic efficacy within 24 hr before study drug administration. Benzodiazepines were allowed as evening sedation on the night prior to surgery (1 mg lorazepam *po* or *sl*).

Patients who satisfied eligibility criteria were randomized in a double-blind fashion to one of five parallel treatment groups. Dolasetron mesylate 25, 50, 100, 200 mg, or placebo were administered *po* one to two hours before induction of general anaesthesia.

All patients received a standardized general anaesthetic. Fentanyl 3 $\mu g \cdot kg^{-1}$ and 0.05 $mg \cdot kg^{-1}$ *d*-tubocurare were administered followed, three minutes later, by 175–500 mg thiopentone and 1.5 $mg \cdot kg^{-1}$ succinylcholine to facilitate tracheal intubation. Anaesthesia was maintained with N_2O (60%), O_2 (40%), isoflurane, and 1 $\mu g \cdot kg^{-1}$ fentanyl prn. Muscle relaxation was maintained with vecuronium (as needed) and was reversed with 0.05 $mg \cdot kg^{-1}$ neostigmine and 0.01 $mg \cdot kg^{-1}$ glycopyrrolate.

For the purpose of this study, a single emetic episode was defined as any one of the following: 1) one or a sequence of vomits in close succession; 2) retching of < five minutes duration combined with a single vomit or; 3) any number of retches in a five minute period.

The occurrence of emetic episodes during the initial 24 hr after surgery was monitored. The severity of nausea and overall patient satisfaction were measured on visual analogue scales (VAS). Vital signs and adverse events were monitored. A 12-lead ECG was performed one hour post-dose (before surgery), in the post-anaesthetic care unit (PACU) as soon after admission as possible, and 24 hr post-dose. At some sites the ECG was repeated again before transfer to the surgical ward and at eight hours post-dose. Electrocardiogram interpretation was standardized through the use of the same model ECG machine (Hewlett Packard Pagewriter Lxi with automatic interpretation of ECG variables) in 12 of the 13 sites. At the 13th site, ECGs were done by the ECG department technicians with a certified 12-lead ECG machine maintained by their department. All ECGs were read centrally by a consultant cardiologist (MJ) who was unaware of the treatment groups. This provided the final interpretation entered into the database.

Nausea was measured using visual analogue scales (VAS) on which "0" was defined as "no nausea" and 100 mm was defined as "nausea as bad as it could be." Patients completed the nausea VAS prior to study drug administration, at discharge from the recovery room, at eight hours post-dose, and at 24 hr post-dose. At each VAS completion the patient was instructed to mark the worst nausea that had occurred since the last VAS.

Patients were also asked to complete a patient satisfaction VAS in which "0" indicated "not at all satisfied" and 100 mm indicated "as satisfied as I could be." This VAS was completed at the completion of the study.

The antiemetic effectiveness of dolasetron mesylate was evaluated at 24 hr post-dose measuring complete response (0 emetic episodes), major response (one emetic episode) and treatment failures (two or more emetic episodes). The timing and administration of rescue therapy was also measured. A patient was eligible for rescue at any time during the 24 hr assessment period if she experienced two or more emetic episodes, persistent nausea for at least 15 min, or if she requested treatment. Adverse events and concomitant medications were also monitored throughout the 24 hr At the final 24 hr assessment, the physical examination, 12-lead ECG, vital signs, and clinical laboratory tests were repeated.

The primary analysis was an intent-to-treat analysis of complete response using logistic regression. Patients prematurely withdrawn were considered failures in the primary analysis of complete response. Logistic regression with a test for linear trend in the proportion of complete responders, controlling for investigator as a main effect, was the primary test of efficacy. The presence of an interaction between investigator and the linear dose response was examined using logistic regression. The covariates defined by previous investigators[10] as significant risk factors for PONV were tested for a significant effect on the likelihood of complete response. Secondary analysis using the Mantel-Haenszel test for non-zero correlation was also performed to confirm the results of the primary analysis. The Cox regression model was used to analyze time to first emetic episode or the use of rescue therapy, whichever occurred first.

Complete response with no nausea was an additional outcome measure defined before unblinding the study. This secondary outcome measure was similarly analyzed with logistic regression techniques. Safety analyses for adverse events were conducted either using logistic regression techniques or a rank analysis of variance controlling for investigator. Differences were considered statistically significant at $P < 0.05$.

Results

Patient characteristics

A total of 374 women were enrolled at 13 investigative sites. One genotypically female patient was undergoing abdominal hysterectomy as the final step in the process to become male and was legally male (but hormonally female) at the time of the study. This patient was included in the primary analysis of efficacy. Of the 374 study patients, one was excluded from the intent-to-treat efficacy analysis because surgery was cancelled after drug administration.

Demographic information is summarized in Table I. There were no differences between groups. There were no differences between treatment groups in the doses of medications used for premedication, induction, maintenance, reversal of muscle relaxation, or postoperative analgesia (Table II).

TABLE I Demographic and baseline characteristics

Variable	*Dose (mg)*				
(mean +/- SD, or %)	*Placebo (n = 75)*	*25 (n = 76)*	*50 (n = 74)*	*100 (n = 74)*	*200 (n = 75)*
Age (yr)	42.5 ± 7.7	43.5 ± 6.9	44.3 ± 8.3	43.7 ± 7.8	42.8 ±8.3
Height (cm)	162.6 ± 6.8	164.5 ± 7.2	163.9 ± 7.1	163.2 ± 6.3	162.7 ± 7.2
Weight (kg)	67.9 ± 14.5	69.5 ± 14.0	71.0 ± 14.8	71.8 ± 14.5	71.2 ± 17.5
ASA I	66.7	63.2	67.6	68.9	56.0
ASA II	33.3	36.8	32.4	31.1	44.0
Race					
Black	4.0	1.3	4.1	8.1	2.7
White	85.3	80.3	85.1	79.7	78.7
Oriental	9.3	13.2	9.5	4.1	16.0
Other	1.3	5.3	1.4	8.1	2.7
History of PONV	53.3	42.1	51.4	43.2	44.0
Previous motion sickness	22.7	28.9	33.8	24.0	28.0
Duration of anaesthesia (hr)	1.5 ± 0.5	1.5 ± 0.5	1.5 ± 0.5	1.5 ± 0.5	1.5 ± 0.5

Efficacy

Efficacy results are summarized in Table III. There was an increase in the proportion of complete responders across the five dose groups ($P = 0.002$). The complete response rate increased from 29.3% in the placebo group to 36.0%, 40.5%, 54.1%, and then decreased to 49.3% in the 25, 50, 100, and 200 mg groups respectively. Both the 100 and 200 mg doses were superior to placebo ($P = 0.003$ and $P = 0.014$ respectively).

A major response was achieved when the patient experienced only one emetic episode, received no rescue medication, and was monitored for at least 23.5 hr after study drug administration. The 100 and 200 mg dose groups were superior to placebo in providing major or complete control of emesis ($P = 0.004$ and $P = 0.013$ respectively). The complete-plus-major response rate was 34.7% in the placebo group while the response rate for dolasetron was 49.3%, 43.2%, 58.1%, and 54.7% for the 25, 50, 100, and 200 mg doses respectively.

Sixty percent of placebo treated patients required rescue medication to supplement the control of their nausea and vomiting compared with 42.7%, 54.1%, 39.2%, and 40% of the patients in the 25, 50, 100, and 200 mg dolasetron groups.

The complete response with no nausea was superior in the 25 mg ($P = 0.03$), 50 mg ($P = 0.035$), 100 mg ($P = 0.001$), and 200 mg ($P = 0.004$) dose groups than placebo. The results of complete response with no nausea are distributed across dose groups as follows: placebo (14.7%), 25 mg (28.0%), 50 mg (28.4%), 100 mg (40.5%), and 200 mg (36.0%). There was an increase in the proportion of complete responders without nausea across the five dose groups ($P = 0.001$).

Patient satisfaction with PONV management as measured by VAS score was consistent with the primary and secondary efficacy outcomes. Patient satisfaction at 24 hr was greater in the 25 mg ($P = 0.048$) and 100 mg ($P = 0.023$) groups than in the placebo group.

Subgroup analyses of the primary efficacy variable revealed that patients who were ASA I, had a previous history of PONV, a previous history of motion sickness, or whose analgesia consisted of < 55 mg morphine in 24 hr, were at increased risk for emetic symptoms. The method of morphine administration (PCA *vs* non-PCA) was not a predictor of complete response. None of these covariates were found to alter the results of the primary analysis of complete response at 24 hr.

Safety

All 374 patients who received a single oral dose of study medication were included in the safety evaluation.

There were no differences between placebo and dolasetron treated patients with respect to adverse events. Table IV summarizes the most frequent adverse events by dose groups which occurred in 1% or more of the study population. The overall rate of adverse events was not changed by dolasetron.

TABLE II Total drugs

Drug (mean +/- SD)	*Placebo*	*Dose (mg) 25*	*50*	*100*	*200*
Fentanyl	291 ± 3	294 ± 115	293 ± 93	286 ± 115	274 ± 6
d-Tubocurare	3 ± 1	3 ± 1	3 ± 1	3 ± 1	3 ± 1
Vecuronium	6 ± 2	5 ± 2	5 ± 2	5 ± 2	5 ± 2
Succinylcholine	5 ± 25	4 ± 19	7 ± 24	8 ± 20	6 ± 23
Thiopentone	323 ± 68	324 ± 71	319 ± 83	326 ± 64	330 ± 71

TABLE III Results

Study drug	*Complete response**	*Complete plus major response†*	*Received escape med*	*Complete response with no nausea‡*	*Patient satisfaction VAS score*
Placebo	29.3	34.6	60.0	14.7	79.0
25 mg	36.0	49.3	42.7	28.0§	91.0§
50 mg	40.5	43.2	54.1	28.4§	89.8
100 mg	54.1§	58.2§	39.2	40.5§	91.0§
200 mg	49.3§	54.6§	40.0	36.0§	85.0

* no emetic episode or rescue for 24 hr

† one or fewer emetic episodes for 24 hr

‡ no emetic episodes, rescue, or nausea for 24 hr

§ $P < 0.05$ *vs* placebo. Results expressed as % except VAS – median.

Two patients who received dolasetron experienced serious adverse events during surgery.

One experienced possible A-V dissociation during peritoneal manipulation. This patient had received 200 mg dolasetron, had a history of hypertension and was being managed with verapamil SR 240 mg daily. Treatment with a vagolytic agent resulted in immediate full recovery of normal rate and rhythm. The other patient received 100 mg dolasetron and experienced nodal bradycardia requiring treatment during a period of traction upon the uterus and peritoneum.

No deaths occurred during the study. There were no clinically important laboratory abnormalities reported in the study with the exception of one patient (25 mg) who had elevated liver enzymes postoperatively that resolved within 10 days of surgery.

There was an increase across doses for lengthening PR interval compared with baseline at 90 min post-dose ($P = 0.001$) and upon arrival in PACU ($P = 0.003$). First degree AV block (PR > 220 msec) occurred in one placebo, one 100 mg, and one 200 mg patient. None of these changes were of clinical importance and none required treatment.

The relationship between the phase of the menstrual cycle and PONV could not be evaluated in this study as most of our patients were having their surgery because of irregular menses.

Discussion

Dolasetron mesylate, a new potent 5-HT_3 receptor antagonist is effective in reducing PONV when given as oral prophylaxis in women undergoing TAH. There was an increase in the proportion of complete responders across the five dose groups. The maximum complete response rate occurred in the 100 mg dose group then decreased in the 200 mg dose group. Three important variables influencing PONV were standardized in this study: type of surgery, sex, and anaesthetic. Previous studies have shown that women are more susceptible to emetic symptoms after surgery and that this increased incidence of PONV is particularly common after gynaecological surgery.[17] Standardization to one type of surgery promotes greater clarity in the interpretation of the results than studies in which multiple surgical procedures have been performed.

Both the 100 mg and 200 mg doses of dolasetron were more effective than placebo in preventing PONV. The complete response rate of 54.1% and 49.3% in the 100 and 200 mg dose groups was similar to recently published results for single dose oral ondansetron. Complete responses for the prevention of PONV were 54% in a European study[18] and 52% in a U.S. study.[19]

All 5-HT_3 receptor antagonists prolong intracardiac conduction. Batanopride (BMY-25801), a 5-HT_3 receptor antagonist investigated as an antiemetic in patients receiving cancer chemotherapy, produced dose-dependent prolongation of QRS and Q-Tc at doses required for antiemetic effect.[20] Ondansetron causes prolongation of Q-Tc in anaesthetized dogs in a dose-dependent fashion but at doses higher than those necessary for its anti-emetic effect.[21] In this study Q-Tc was not affected by clinically effective doses of dolasetron. The QRS interval prolongation showed a linear trend but this was seen in a small number of patients who remained asymptomatic and required no treatment. Ondansetron[22] and dolasetron have shown minimal haemodynamic effects in surgical patients.

One serious adverse event deserves further comment. This patient was in first degree AV-block before receiving 200 mg dolasetron. She was also taking 240 mg verapamil SR for treatment of hypertension. During peritoneal manipulation the patient developed severe bradycardia associated with A-V dissociation of short duration. This event suggests the possibility of an interaction between 5-HT_3 antagonists and agents that affect cardiac conduction. This merits further evaluation. Peritoneal manipulation itself is sometimes associated with profound bradycardia and cannot be eliminated as a causal factor in this report.

TABLE IV Frequency (%) of most frequent adverse events

(Incidence > 1% study population)

	Placebo (n = 75)	*Dose (mg) 25 (n = 76)*	*50 (n = 74)*	*0 (n = 74)*	*200 (n=75)*
Pruritus	8.0	.5	13.5	8.1	16.0
Headache	4.0	9.2	12.2	9.5	8.0
Bradycardia	5.3	14.5	6.8	8.1	6.7
Hypotension	8.0	9.2	6.8	2.7	12.0
Dizziness	0.0	6.6	5.4	8.1	5.3

The incidence of dizziness in the dolasetron groups from this study was 6.4%. This could be a function of a combination of factors: concurrent hypotension related to anaesthesia or opioid use or movement to a prone position after prolonged supine bed rest. Dizziness has also been reported in phase I (13%) and phase II (5%) dolasetron studies as well as following a single oral dose of ondansetron for the prevention of emetic symptoms (3.4%).[19]

Droperidol, ondansetron, granisetron, transdermal scopolamine, and most recently perphenazine[23] are effective in preventing PONV. In that recent study, droperidol, ondansetron, and perphenazine were equally effective in reducing PONV for the first four hours after surgery but the authors concluded that perphenazine was the drug of choice because of its low cost and low incidence of side-effects. Other studies comparing the effectiveness of 5-HT_3 receptor antagonists with other antiemetics over a longer duration of follow-up are needed.

Post-operative nausea and vomiting is a complex problem which is affected by multiple factors: sex, type of surgery, opioids, pain, positioning, co-existing disease, concomitant medication, phase of the menstrual cycle, and patient weight. Drugs of many classes have been used singly both for the prevention and treatment of PONV. Few studies exist using combination therapy in an effort to optimize the varying actions of different classes of drugs. A recent study[24] suggests that the $5HT_3$-antagonist, granisetron, in combination with dexamethasone is superior to granisetron alone in reducing PONV in patients undergoing major gynaecological surgery. Future studies should address the effectiveness and costs of combination therapy.

Is prophylaxis of PONV a reasonable medical intervention? No studies exist that show a reduced length of hospital stay for inpatients receiving prophylaxis. There is a widespread assumption that prevention of PONV might lead to earlier discharge for ambulatory surgical patients and a reduced incidence of unexpected hospital admission but no studies exist to support this belief.[25] Despite the lack of evidence of the economic advantages of PONV prophylaxis, most volunteers, when questioned, fear anaesthesia/surgery induced nausea and vomiting.[5] Drugs that may reduce this unpleasant aspect of surgical intervention are needed. For the time being it seems reasonable to offer patients with a high likelihood for developing PONV an attempt at prophylaxis. For patients in high risk groups, prophylaxis of PONV offers a potential improvement in their surgical experience.

In summary, both 100 mg and 200 mg dolasetron mesylate administered *po* as a single dose one to two hours before induction of general anaesthesia are effective in reducing PONV in women undergoing TAH. The 100 mg dose had the greatest complete response rate and was well tolerated and safe.

Acknowledgments

The authors wish to acknowledge the invaluable work done by our study coordinators:

1. Gail Commandant (Edmonton)
2. Pat Corey-Plett (Winnipeg)
3. Christiane Côté (Sherbrooke)
4. Cindy Dziwenko-Cox (Edmonton)
5. Cathy Edstrom (Edmonton)
6. Carolyn Franke (Toronto)
7. Jack Kress (Winnipeg)
8. Hedy Papenburg (Montréal)
9. Madelaine Pilote (Sherbrooke)
10. Terri-Lynn Ronaghan (Vancouver)
11. Anne-Marie Tkachuk (Vancouver)
12. Sally Tufts (Halifax)

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