Intravenous dolasetron mesilate ameliorates postoperative nausea and vomiting

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Purpose: To compare the efficacy, safety, and tolerability of dolasetron mesilate with placebo for the treatment of postoperative nausea and vomiting (PONV).

Methods: In a randomized, multicentre, double-blind, placebo-controlled study 337 adult patients undergoing surgery with general anaesthesia received one of four single, doses of dolasetron mesilate *iv* (12.5, 25, 50, or 100 mg) or placebo. Study medication was administered postoperatively when the patient reported nausea lasting 10 min or when one emetic episode occurred within two hours of the patient's arrival in the recovery room. Efficacy was assessed by the investigators over the 24-hr study period by recording the number and timing of emetic episodes, the severity of nausea, the timing of administration of escape antiemetic medications, and patients' and investigators' satisfaction with antiemetic therapy.

Results: The study sample was predominately women, and the surgical procedures were primarily gynaecological. All dolasetron mesilate doses produced higher complete response rates than placebo ($P<0.05$). Only approximately one-third of dolasetron patients required escape antiemetic medication compared with more than 50% of patients in the placebo group. Both patient and physician satisfaction with dolasetron treatment was high. The most common adverse event was mild or moderate headache for both placebo-treated patients and dolasetron-treated patients. Clinical laboratory results were unremarkable.

Conclusion: Single doses of dolasetron mesilate *iv*, given after the first episode of PONV, were both effective and safe in this adult patient population.

Objectif : Comparer l'efficacité, la sécurité et l'acceptabilité du mésilate de dolasetron avec celles d'un placebo pour le traitement des nausées et vomissements postopératoires (NVPO).

Méthodes : Au cours d'une étude multicentrique, en double aveugle, contrôlée par placebo, 337 adultes soumis à une chirurgie sous anesthésie générale ont reçu du mésilate de dolasetron à une de quatre posologies *iv* (12,5, 25, 50, ou 100 mg) ou un placebo. Le médicament était administré en postopératoire lorsque le patient se plaignait d'une nausée de durée 10 min ou quand au moins en épisode émétique survenait au cours des deux heures suivant l'arrivée du patient en salle de réveil. Sur une période d'étude de 24 h, l'efficacité était évaluée par les investigateurs par l'enregistrement du nombre et de la chronologie des épisodes, la gravité de la nausée, le temps de l'administration de la médication antiémétique de rattrapage, et la satisfaction du patient ou de l'investigateur envers le traitement.

Résultats : L'échantillon de la population étudiée comprenait surtout des femmes et les interventions étaient surtout gynécologiques. Toutes les doses de mésilate de dolasetron procuraient une réponse complète plus fréquente que le placebo ($P<0,05$). Seulement un tiers environ des patients sous dolasetron ont eu besoin d'un médicament antiémétique de rattrapage comparativement à plus de 50% du groupe placebo. La satisfaction du chirurgien et de l'anesthésiste à l'égard de la prévention réalisée par le dolasetron était élevée. Une céphalée légère ou modérée constituait la réaction défavorable la plus fréquente tant chez les patients sous placebo que sous dolasetron. Les résultats des examens de laboratoire étaient non significatifs.

Conclusion : Chez une population adulte, les doses uniques de mésilate de dolasetron *iv* administrées après un premier épisode de NVPO sont à la fois efficaces et bien tolérées.

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ALTHOUGH the incidence of nausea and vomiting after surgery with general anaesthesia has decreased considerably in recent years, due to the use of perianaesthetic medications and anaesthetic techniques that are much less emetogenic than their predecessors,[1,2] episodes of postoperative nausea and vomiting (PONV) are not only extremely unpleasant for the patient,[3,4] but can also prolong recovery time. In some cases, PONV may directly result in readmission to the hospital.[5] Consequently, every effort is employed to alleviate the potential for PONV.

Because of the variable efficacy and potential adverse effects (eg, hypotension, prolonged recovery from anaesthesia, extrapyramidal reactions) associated with traditional antiemetic agents, routine prophylaxis of PONV has been generally unwarranted.[1] However, the development of agents that selectively block the response to serotonin (5-HT) at 5-HT_3 receptors has provided more effective options for the prevention and treatment of PONV.[6] Unfortunately, few direct comparisons of the 5-HT_3 antagonists and other traditional antiemetic regimens have been conducted to date. Therefore, the role of the 5-HT_3 antagonists in preventing and treating PONV is still evolving.

Dolasetron mesilate (MDL 73,147EF, Anzemet,® Hoechst Marion Roussel) is a new potent and selective 5-HT_3 antagonist[7,8] undergoing clinical investigation as an antiemetic agent. Oral and intravenous (*iv*) formulations have been shown to be well tolerated in normal volunteers[9–11] and numerous double-blind, randomized studies have demonstrated that dolasetron possesses excellent efficacy in the prevention of chemotherapy-induced nausea and vomiting when given as a single *iv* dose.[12–16] Recently completed multicentre trials have also demonstrated that dolasetron has considerable efficacy for the *prevention* of PONV in females undergoing outpatient laparoscopic gynaecologic surgery[17] and for the *treatment* of PONV in adults after outpatient surgery under general anaesthesia.[18]

The present study was undertaken to evaluate the safety and antiemetic efficacy of single *iv* doses of dolasetron mesilate for the treatment of PONV in patients who had surgery under general anaesthesia. The anaesthetic technique and perianaesthetic medications used were standardized among participating clinical centres.

Methods

Study design

All patients signed a written statement of informed consent prior to conduct of the study and the study protocol was approved by the Institutional Review Board at each of the participating clinical centres. This multicentre, randomized, double-blind, placebo-controlled, parallel group trial compared the efficacy, safety, and tolerability of four single *iv* doses of dolasetron mesilate (12.5, 25, 50, and 100 mg) with placebo for the treatment of PONV associated with recovery from general anaesthesia. The dolasetron mesilate doses utilized in this study are equivalent to 9.3, 18.5, 37, and 74 mg of dolasetron base. Each dose of dolasetron mesilate was diluted to a total volume of 50 ml with normal saline and administered *iv* over five minutes. The start of the study period (t_0) was defined as the beginning of the placebo or dolasetron infusion. Study medication (dolasetron or placebo) was administered postoperatively when the patient reported nausea lasting at least 10 min or when one or more emetic episodes (ie, vomiting or retching) occurred within two hours of the patient's arrival in the recovery room. Efficacy and safety were assessed for 24 hr after study drug administration.

Patients

Eligible patients were men or women, 18 to 65 yr of age, who were scheduled for surgery and received general anaesthesia. Anaesthetic/analgesic agents acceptable for use before, during, and after surgery are listed in Table I. All patients were American Society of Anaesthesiologists (ASA) physical class I or II; had no addiction to alcohol or other substances; and had normal pre-study serum sodium and potassium concentrations and pre-study SGOT/SGPT concentrations less than twice the upper limit of normal.

Patients were excluded from study participation if they were pregnant or breast feeding; had clinically

TABLE I Agents acceptable for use before, during, and after surgery

Premedication	*Induction/Maintenance*	*Postoperative Analgesia*
Any benzodiazepine	Thiopentone	Proppacetamol
	Nitrous oxide in oxygen	Morphine
	Isoflurane	Buprenorphine
	Enflurane	NSAIDs
	Atracurium	
	Pancuronium	
	Succinylcholine	
	Vecuronium	
	Fentanyl	
	Sufentanil	
	Alfentanyl	
	Atropine	
	Neostigmine	
	Glycopyrrolate	

There were no demographic differences among the treatment groups.

important major organ system dysfunction or pre-study clinical laboratory abnormalities; had experienced vomiting within 24 hr of surgery or exhibited vomiting secondary to an organic aetiology (eg, bowel obstruction); required postoperative placement of an intragastric tube; required treatment with potential antiemetics (ondansetron, granisetron, metoclopramide, domperidone, thiethylperazine, promethazine, hydroxyzine, trimethobenzamide, prochlorperazine, droperidol, tricyclic antidepressants, diphenhydramine, corticosteroids, fluoxetine, scopolamine, or ephedrine) in the 24 hr before study drug administration; had received any investigational drug in the previous 21 days; or had received previous treatment with dolasetron.

Efficacy evaluations

Efficacy was assessed by the investigators over the 24-hr study period on an intent-to-treat basis by recording the number and timing of emetic episodes, the severity of nausea, the timing of administration of escape antiemetic medications, and patients' and investigators' satisfaction with antiemetic therapy. A *complete response* to study treatment was defined as no emetic episodes during the 24-hr postdosing observation period and no requirement for escape antiemetic medication. Patients had to be monitored for at least 24 hr after dosing to qualify as complete responders. Patients not meeting these criteria were classified as treatment failures.

The timing of escape antiemetic medication was measured in reference to the administration of study medication (t_0). Patients qualified for escape antiemetic medication if they demonstrated at least one emetic episode beyond the first 30 min after dosing or if they specifically requested it as a result of moderate to severe nausea. Escape antiemetic medication consisted of the standard regimen utilized by the individual clinical centers.

The severity of nausea was measured by a visual analog scale (VAS) and a discrete scale (DS). The nausea VAS ranged from 0 to 100 mm, with 0 representing 'no nausea' and 100 representing 'nausea as bad as it can be.' Nausea was assessed as soon as the patient demonstrated orientation in time, place, and person. The nausea VAS was completed prior to administration of study medication and every hour the patient was awake during the first eight hours after dosing. The DS evaluation consisted of the investigator's rating of the patient's maximum severity of nausea on a scale of 0 to 3, with 0 representing 'no nausea' and 3 representing 'severe nausea.'

Overall patient satisfaction with assigned therapy was assessed 24 hr after the administration of study medication by a VAS that ranged from 0 to 100 mm with 0 representing 'not at all satisfied' with treatment and 100 indicating 'complete satisfaction' with treatment. The investigators' global assessment of antiemetic efficacy was made 24 hr after dosing on a rating scale ranging from 0 to 3; a rating of 0 indicated 'no efficacy' for the assigned treatment while a rating of 3 indicated 'excellent efficacy.'

Safety evaluations

The safety analysis included all patients receiving study medication and consisted of adverse event reports, clinical laboratory results (haematology, blood chemistry, urinalysis), vital signs (pulse, respiratory rate, and recumbent blood pressure), physical examination data, ECG results, and an assessment of the patient's recovery score (motor activity, respiration, circulation, consciousness, and skin color).

Statistical methodology

Patients were randomly assigned to one of the five treatment groups when their eligibility for the study was confirmed postoperatively. Potential differences among the five treatment groups with respect to baseline characteristics were examined by analysis of variance (ANOVA) for quantitative variables and logistic regression analysis for qualitative variables.

The primary efficacy endpoint was the number of complete responders in each treatment group. Comparison between placebo and the overall dolasetron-treated population was made by means of logistic regression, controlling for investigator as a main effect. Dose-related trends in complete response rate for dolasetron also were evaluated by logistic regression.

The time to first emetic episode or use of escape antiemetic medication was analyzed using the Cox regression model and differences among treatment groups were assessed using the hazard ratios. Nausea VAS scores (changes from baseline in postdose maximum) were evaluated using analysis of covariance, controlling for investigator and degree of baseline nausea. The proportion of patients reporting no nausea (postdose maximum <5mm) in the first eight hours after dosing was compared for placebo patients and all patients who received dolasetron. The assessment of nausea by investigators and the investigators' global assessment of efficacy were evaluated by a Mantel-Haenszel row mean scores test using modified ridit scores to compare placebo with the total dolasetron group. Patient satisfaction VAS scores were compared (placebo *vs* total dolasetron group) using a two-way rank ANOVA controlling for investigator.

Subgroup analyses were conducted by logistic regression to determine the effect of gender, age, weight,

ASA status, previous history of PONV, type of surgery, duration of anaesthesia, total morphine dose, time between end of anaesthesia and study drug administration, and fentanyl dose on the likelihood of a complete response.

Analyses of the frequencies of adverse events by dolasetron mesilate dose were accomplished by logistic regression. Changes in vital signs, clinical laboratory variables, and ECG parameters were assessed by ANOVA and tests for linear trend with dolasetron mesilate dose.

Results

A total of 337 patients were treated at 19 clinical centres in Europe. Six of the centres entered 77% of the patients (261/337), with the remaining centres contributing 1 to 12 patients each. Demographic and baseline characteristics for the patients enrolled in the study are summarized in Table II. There were no differences among the five treatment groups for any of these variables. Women comprised 94.7% (319/337) of the study population, gynaecological surgery was most common (210/337, 62.3%), and patients were primarily ASA status 1 (295/337, 87.5%). More than half of the patients (180/337, 53.4%) reported both nausea and vomiting prior to study drug administration, and 45.8% of patients (154/337), slightly less than half, had a previous history of PONV. The duration of anaesthesia averaged 1.73 hr for the total study population. Concomitant medication usage was similar for the five treatment groups. Metoclopramide (84/337, 24.9%) and prochlorperazine (39/337, 11.6%) were most commonly used as escape antiemetic medications. Patients who received prohibited medications with known antiemetic activity were considered major protocol violators but were included in the primary intent-to-treat analyses of efficacy.

Efficacy

Complete responses were achieved by 24.2%, 27.7%, 37.3%, and 25.0% of patients who received 12.5, 25, 50, and 100 mg of dolasetron mesilate, respectively. When compared with the placebo group in which 11.3% of patients achieved a complete response, the complete response rates were higher for all of the individual dolasetron treatment groups ($P < 0.05$) (Figure 1).

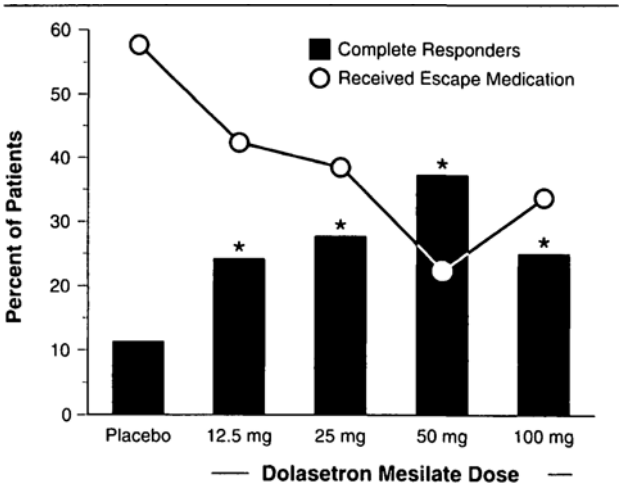

FIGURE 1 The percentage of complete responders (bars) and the percentage of patients who required escape antiemetic medication (line) over the 24-hr study period. (*) denotes statistically significant differences in complete response compared with placebo, $P < 0.05$.

TABLE II Demographic characteristics and baseline variables by treatment group

Dolasetron Mesilate Dose (mg)						
Variable	*Placebo (n=71)*	*12.5 (n=66)*	*25 (n=65)*	*50 (n=67)*	*100 (n=68)*	*Total (n=337)*
Gender (%)						
Male	4 (5.6%)	3 (4.5%)	3 (4.6%)	5 (7.5%)	3 (4.4%)	18 (5.3%)
Female	67 (94.4%)	63 (95.5%)	62 (95.4%)	62 (92.5%)	65 (95.6%)	319 (94.7%)
Mean Age (yr) ± SD	38 ± 10	42 ± 13	40 ± 11	41 ± 10	41 ± 10	40 ± 11
Mean Height (cm) ± SD	165 ± 8	164 ± 8	164 ± 7	164 ± 8	162 ± 7	164 ± 8
Mean Weight (kg) ± SD	65 ± 12	65 ± 12	63 ± 12	65 ± 13	63 ± 11	64 ± 12
Prior History of PONV	34 (47.9%)	35 (53.0%)	30 (46.2%)	(44.8%)	25 (37.3%)	154 (45.8%)
Type of Surgery						
Gynaecological	40 (56.3%)	43 (65.2%)	38 (58.5%)	45 (67.2%)	44 (64.7%)	210 (62.3%)
Other	31 (43.7%)	23 (34.8%)	27 (41.5%)	22 (32.8%)	24 (35.3%)	127 (37.7%)
Mean Duration of Anaesthesia (hr) ± SD	1.6 ± 0.9	1.8 ± 0.8	1.8 ± 1.0	1.7 ± 0.9	1.7 ± 0.9	1.7 ± 0.9
Mean Time to First Emetic Episode After Start of Anaesthesia (hr) ± SD	2.5 ± 1.0	2.7 ± 0.9	2.6 ± 1.1	2.7 ± 1.0	2.8 ± 1.1	2.6 ± 1.0

There were no demographic differences among the treatment groups.

A higher percentage of placebo patients received escape antiemetic medications than did dolasetron patients. Kaplan-Meier survival curves for the time to first emetic episode or use of escape antiemetic medication (placebo *vs* dolasetron treatment groups) are shown in Figure 2. Virtually all dolasetron patients who experienced an emetic episode or required escape antiemetic medication did so within the first 12 hr after dosing. Further, when compared individually with placebo, patients who received 12.5, 25, and 50 mg of dolasetron mesilate had longer times to the first emetic episode or use of escape antiemetic medication ($P<0.05$).

Subgroup analyses on various factors that might predict the likelihood of a complete response revealed effects for a number of variables, including age, criteria for study eligibility (ie, nausea alone or with an emetic episode), duration of anaesthesia, time from cessation of anaesthesia to study drug administration, and the total doses of morphine and fentanyl administered ($P<0.05$) (Table III). Patients were less likely to have a complete response if they were older, had longer anaesthesia, received study drug soon after cessation of anaesthesia, and received larger doses of fentanyl or morphine. Those patients who experienced either vomiting or a combination of nausea and vomiting before study entry were less likely to have a complete response than patients who had only nausea before study entry. Although the association was not statistically significant, patients with a previous history of PONV tended to be less likely to have a complete response. Other variables (weight, gender, and type of surgery) showed no association with the probability of a complete response. The difference of dolasetron over placebo was maintained when controlling for the effects of any of these subgroups.

Patient nausea VAS scores are summarized in Table IV. At hour 0, just before study drug administration, a substantial degree of nausea was noted for all five treatment groups. Patients' maximum nausea VAS scores were then determined in the eight hours after study drug administration. All doses of dolasetron mesilate produced lower post-dose maximum nausea VAS scores than did placebo ($P<0.05$). In addition, a greater percentage of patients reported no nausea after 12.5, 25, and 100 mg of dolasetron mesilate than after placebo in the eight hours after dosing ($P<0.05$). No nausea was reported by 28.8%, 24.6%, 22.4%, and 25.0% of patients who received 12.5, 25, 50, and 100 mg of dolasetron mesilate, respectively, and only 11.3% of placebo-treated patients. No differences were noted among the dolasetron treatment groups for nausea VAS scores or for the percentage of patients reporting no nausea. Further, patient satisfaction VAS ratings demonstrated that dolasetron-treated patients were more satisfied with their treatment than patients who were given placebo ($P=0.003$).

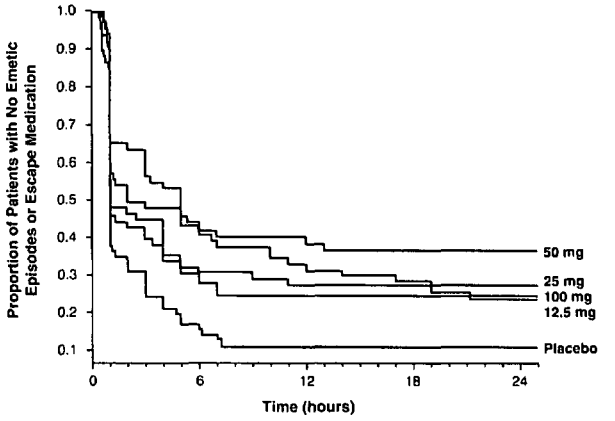

FIGURE 2 Kaplan-Meier survival curves for time to first emetic episode or first use of escape antiemetic medication for the placebo and dolasetron treatment groups.

Investigators' ratings of the overall severity of patients' nausea according to the nausea DS demonstrated that patients who received placebo were more likely to be nauseated than patients who received dolasetron (45.1% with 'severe nausea' versus 32.5%, respectively) ($P=0.006$). Patients who received dolasetron were more likely to have 'no nausea' than placebo patients according to investigators' evaluations. When the investigators' ratings of overall efficacy were analyzed, patients treated with dolasetron were more likely to receive higher efficacy ratings than patients in the placebo group (32.7% with 'excellent' *vs* 18.3%, respectively) ($P<0.001$).

Safety

The majority of adverse events reported in this study were mild or moderate in intensity. Overall, the rate of adverse events was 18.3% (13/71) in the placebo group and 18.2% (12/66), 15.4% (10/65), 29.9% (20/67), and 29.4% (20/68) in the 12.5, 25, 50, and 100-mg dolasetron mesilate treatment groups, respectively. No patient discontinued participation in this study prematurely as a result of any adverse event.

Headache was the most commonly reported adverse event in each of the treatment groups (Table V). However, no dose-related trends for the incidence of headache were observed with dolasetron. The frequency of other adverse events was considerably lower than that for headache, and no dose-related trends could be ascertained (Table V). Of the reported nonspecific

TABLE III Complete response by subgroups

			Dolasetron Mesilate Dose (mg)			
Subgroup	*Placebo (n=71)*	*12.5 (n=66)*	*25 (n=65)*	*50 (n=67)*	*100 (n=68)*	*P-values*
Age						0.021
≤40 yr (n=167)	5/42 (11.9%)	9/28 (32.1%)	10/32 (31.3%)	13/33 (39.4%)	9/32 (28.1%)	
>40 yr (n=170)	3/29 (10.3%	7/38 (18.4%)	8/33 (24.2%)	12/34 (35.3%)	8/36 (22.2%)	
Weight						0.872
≤62 kg (n=173)	4/35 (11.4%)	5/34 (14.7%)	10/37 (27.0%)	12/33 (36.4%)	6/34 (17.6%)	
>62 kg (n=164)	4/36 (11.1%)	11/32 (34.4%)	8/28 (28.6%)	13/34 (38.2%)	11/34 (32.4%)	
Previous History of PONV						0.091
No (n=182)	5/37 (13.5%)	10/31 (32.3%)	12/35 (34.3%)	16/37 (43.2%)	10/42 (23.8%)	
Yes (n=154)	3/34 (8.8%)	6/35 (17.1%)	6/30 (20.0%)	9/30 (30.0%)	7/25 (28.0%)	
Type of Surgery						0.581
Gynaecological (n=210)	4/40 (10.0%)	7/43 (16.3%)	8/38 (21.1%)	14/45 (31.1%)	12/44 (27.3%)	
Other (n=127)	4/31 (12.9%)	9/23 (39.1%)	10/27 (37.0%)	11/22 (50.0%)	5/24 (20.8%)	
Gender						0.478
Women (n=319)	7/67 (10.4%)	15/63 (23.8%)	18/62 (29.0%)	21/62 (33.9%)	16/65 (24.6%)	
Men (n=18)	1/4 (25.0%)	1/3 (33.3%)	0/3 (0.0%)	4/5 (80.0%)	1/3 (33.3%)	
Time Between Cessation of Anaesthesia and Study Drug Administration						0.003
≤1 hr (n=181)	4/38 (10.5%)	9/37 (24.3%)	7/39 (17.9%)	10/34 (29.4%)	5/33 (15.2%)	
>1 hr (n=156)	4/33 (12.1%)	7/29 (24.1%)	11/26 (42.3%)	15/33 (45.5%)	12/35 (34.3%)	
Duration of Anaesthesia						0.003
≤1 hr (n=71)	4/18 (22.2%)	4/11 (36.4%)	4/13 (30.8%)	9/15 (60.0%)	4/14 (28.6%)	
>1 hr (n=266)	4/53 (7.5%)	12/55 (21.8%)	14/52 (26.9%)	16/52 (30.8%)	13/54 (24.1%)	
Total Morphine Dose						0.018
≤10 mg (n=274)	7/59 (11.9%)	16/54 (29.6%)	17/52 (32.7%)	21/57 (36.8%)	12/52 (23.1%)	
>10 mg (n=63)	1/12 (8.3%)	0/12 (0.0%)	1/13 (7.7%)	4/10 (40.0%)	5/16 (31.3%)	
Total Fentanyl Dose						<0.001
≤250 μg (n=174)	4/36 (11.1%)	12/28 (42.9%)	14/37 (37.8%)	16/36 (44.4%)	10/37 (27.0%)	
>250 μg (n=163)	4/35 (11.4%)	4/38 (10.5%)	4/28 (14.3%)	9/31 (29.0%)	7/31 (22.6%)	
Eligibility Criteria						0.033
Nausea Only (n=54)	4/10 (40.0%)	3/10 (30.0%)	5/17 (29.4%)	4/8 (50.0%)	3/9 (33.3%)	
Vomiting Only (n=103)	1/17 (5.9%)	8/22 (36.4%)	4/16 (25.0%)	10/24 (41.7%)	6/24 (25.0%)	
Nausea and Vomiting (n=180)	3/44 (6.8%)	5/34 (14.7%)	9/32 (28.1%)	11/35 31.4%)	8/35 (22.9%)	

TABLE IV Summary of patient nausea vas scores

	Dolasetron Mesilate Dose (mg)				
Time Point	*Placebo (n=71)*	*12.5 (n=66)*	*25 (n=65)*	*50 (n=67)*	*100 (n=68)*
Hour 0	(n=53)	(n=53)	(n=50)	(n=51)	(n=54)
Median VAS Scores (mm)	83.0	86.0	83.5	89.0	90.0
Maximum Over Hours 1 to 8	(n=71)	(n=66)	(n=65)	(n=67)	(n=68)
Median VAS Scores (mm)	67.0	34.0	31.0	32.0	31.0
P values for Comparison to Placebo	<0.001	<0.001	0.01	<0.001	0.016

TABLE V Frequency of adverse events reported by >2% of patients

	Dolasetron Mesilate Dose (mg)				
Adverse Event	*Placebo (n=71)*	*12.5 (n=66)*	*25 (n=65)*	*50 (n=67)*	*100 (n=68)*
	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*
Headache	4 (5.6)	7 (10.6)	4 (6.2)	7 (10.4)	10 (14.7)
Injection Site Pain	1 (1.4)	0	1 (1.5)	3 (4.5)	1 (1.5)
ECG Abnormal (nonspecific)	0	1 (1.5)	0	2 (3.0)	1 (1.5)
Hypertension	1 (1.4)	1 (1.5)	0	2 (3.0)	0
Hypotension	0	0	0	1 (1.5)	2 (2.9)

ECG changes 24 hr post-dose, all were mild or moderate in nature and none were considered clinically important by investigators. In this study, ECGs were obtained 24 hr post-dosing, and no dose-related, mean changes from baseline in heart rate, PR interval, QRS duration, QT interval, QT_c or JT interval were observed.

Statistical analysis of clinical laboratory data revealed that several variables exhibited dose-related trends. Clinical laboratory data were also unremarkable; changes from baseline that did achieve statistical significance generally represented only small deviations from the laboratory normal ranges and were not associated with any clinical importance.

Discussion

This randomized, multicentre, double-blind, placebo-controlled trial demonstrated that single *iv* doses of dolasetron mesilate relieve PONV in adults after surgery under general anaesthesia. All dolasetron mesilate doses in this study produced higher proportions of complete responses than did placebo. However, no additional benefit in the antiemetic response to dolasetron mesilate was observed at the highest dose (100 mg) used in this study. In addition, patients treated with dolasetron were more satisfied with their treatment, had less nausea, and had less need for escape antiemetic medications than patients who received placebo.

The efficacy of dolasetron observed in our study compares favourably with other recently conducted studies with dolasetron for the prevention and treatment of PONV. In a recently reported study[17] that evaluated four single *iv* doses of dolasetron mesilate for the prevention of PONV in women undergoing outpatient laparoscopic surgery, all doses tested (12.5, 25, and 50 mg) prevented PONV compared with placebo; however, there was no additional benefit in complete responses to dolasetron mesilate for doses >12.5 mg. The results of a study conducted in the United States that evaluated the same doses used in our study for the treatment of established PONV after surgery have also been reported recently.[18] Kovac *et al.* demonstrated complete response rates for dolasetron mesilate 24 hours after drug treatment of 35% for the 12.5-mg group, 28% for the 25-mg group, 29% for the 50-mg group, and 29% for the 100-mg group. Although the complete response rates observed in our study were representative of a bell-shaped curve rather than the plateau effect demonstrated in the Kovac study, the trends of the two studies were similar; there was no additional benefit in patients who received doses higher than 12.5 mg of

dolasetron mesilate. In addition, in both our study and the US study, placebo patients had complete response rates of only 11% and patient nausea VAS scores were similar.

Numerous studies have been conducted to evaluate the antiemetic efficacy of another 5-HT_3 antagonist, ondansetron, for the prevention and treatment of PONV.[19-25] The results observed in our study compare favourably with the results obtained with ondansetron for the treatment of PONV.[19,22,25]

Patient and physician satisfaction with dolasetron therapy was high. This undoubtedly reflects both the drug's antiemetic efficacy and the relative absence of severe adverse events. Dolasetron was well tolerated in our study with mild or moderate headache the most commonly observed adverse event. Headache is a common consequence of administration of 5-HT_3 receptor antagonists; it has been reported in studies with ondansetron,[26,27] granisetron,[28] and tropisetron.[29] The frequency of headache in our study was lower than that traditionally reported for ondansetron.[30,31]

In conclusion, this controlled study confirms the effectiveness of dolasetron for the treatment of PONV in adult patients undergoing surgery with general anaesthesia. The efficacy of dolasetron is consistent with results obtained in other studies with other 5-HT_3 antagonists, and patient satisfaction and tolerability of dolasetron was high in this study. While the 50 mg dose of dolasetron mesilate appeared to produce the highest complete response rates in our study, other dolasetron studies[17,18] have shown that doses >12.5 mg do not offer any additional benefit. Further studies to identify the lowest effective dose of dolasetron appear to be warranted. Finally, specific targeting of those individuals who would be most likely to experience nausea and vomiting, based on a previous history of PONV or prognostic demographic variables, would optimize the use of a 5-HT_3 antagonist antiemetic in this patient population.[32,33]

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