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Original Paper

Therapeutic Equivalence of Single Oral Doses of Dolasetron Mesilate and Multiple Doses of Ondansetron for the Prevention of Emesis After Moderately Emetogenic Chemotherapy

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This multicentre, randomised, double-blind study was designed to compare the anti-emetic efficacy and safety of single oral doses of dolasetron mesilate with that of the approved oral, multiple-dose regimen of ondansetron in 399 cancer patients receiving moderately emetogenic chemotherapy. Single oral doses of 25, 50, 100 or 200 mg of dolasetron mesilate were administered 1 h prior to the initiation of moderately emetogenic chemotherapy. Multiple doses of ondansetron (8 mg × 3 or 8 mg × 4) capsules, or matching placebo for patients randomised to dolasetron, were given 1.5 h before and 6.5, 14.5 and 22.5 h after the start of chemotherapy (total dose = 32 mg). Efficacy was evaluated for 24 h after the initiation of chemotherapy. The most frequently used moderately emetogenic chemotherapeutic agents included cyclophosphamide, doxorubicin and carboplatin (28.4, 23.1 and 20.6% of patients, respectively). A statistically significant ($P < 0.001$) linear dose–response relationship was observed over the entire dolasetron dosage range for all efficacy parameters. Complete response rates were 45.0, 49.4, 60.5 and 76.3% for 25, 50, 100 and 200 mg dolasetron mesilate, respectively, and 72.3% of ondansetron patients. A single oral 200 mg dolasetron mesilate dose was therapeutically equivalent to ondansetron for all efficacy parameters and patient satisfaction was high. Overall, there were no significant differences in the incidence of adverse events between any of the dolasetron mesilate doses, or between dolasetron and ondansetron. Headache was most frequently reported (approximately 15% for each drug). No clinically important changes in vital signs or clinical laboratory parameters were observed with either drug. In conclusion, a single oral 200 mg dolasetron mesilate dose was therapeutically equivalent to multiple-dose ondansetron in the prevention of emesis and nausea following moderately emetogenic chemotherapy.

Key words: anti-emetic, carboplatin, clinical trial, cyclophosphamide, dolasetron, doxorubicin, emesis, nausea, ondansetron, 5-HT$_3$ receptor antagonist
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INTRODUCTION

CHEMOTHERAPY-INDUCED nausea and vomiting are the most feared and severe side-effects reported by patients and their physicians, specialists and nurses [1–3]. It is well recognised that the type, dose and route of administration of chemotherapeutic agents are important prognostic factors influencing the emetogenic potential of chemotherapy and emetogenicity is additive in patients receiving combination chemotherapy [4, 5]. While no single agents have been shown to be 100% effective in controlling chemotherapy-induced nausea and

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vomiting, serotonin$_3$ (5-HT$_3$) receptor antagonists are considered to be as effective as traditional therapies, such as metoclopramide, without the risk of extrapyramidal side-effects [5, 6].

Dolasetron mesilate (Anzemet®, MDL 73,147EF, Hoechst Marion Roussel, Inc., Kansas City, Missouri, U.S.A.) is a new anti-emetic agent that is highly selective for 5-HT$_3$ receptors and is a potent 5-HT$_3$ receptor antagonist [7–9]. Dolasetron is rapidly and extensively reduced to a 50-fold more potent and more selective metabolite (MDL 74,156) that possesses a longer half-life [10, 11]. Development of drug dosing for dolasetron was based on the mesilate salt. Therefore, all references to dolasetron mesilate dose refer to the salt and adjustments for the equivalent base require multiplying the dose of mesilate salt by 0.74.

Two phase I studies with oral dolasetron have been conducted in healthy male volunteers [12, 13]. Single oral doses of dolasetron mesilate ranging from 50 to 400 mg [12] and doses of 25 to 50 mg twice a day for 7 days [13] were well tolerated in two separate studies. Headache, lightheadedness, increased appetite, tiredness and gastrointestinal symptoms were most commonly reported. The incidence of these events was similar to that reported for other 5-HT$_3$ antagonists [6].

Numerous dose-ranging studies with single intravenous doses of dolasetron mesilate in patients receiving highly or moderately emetogenic chemotherapy have established the efficacy, safety and large therapeutic index for dolasetron [14–18]. Randomised, double-blind trials comparing various doses and dose regimens have confirmed the anti-emetic efficacy of dolasetron mesilate when administered as a single intravenous dose [19–21]; multiple dosing did not confer any significant advantages over the single doses tested.

Recently, Rubenstein and associates [22] reported on the results of a dose-ranging trial using four different single oral doses of dolasetron mesilate for the prevention of emesis in cancer patients receiving moderately emetogenic chemotherapy. A significant linear trend across the four doses (25, 50, 100 or 200 mg) was apparent for complete response and patient evaluations of nausea control and treatment satisfaction. Single oral doses of dolasetron mesilate were well tolerated [22].

This multicentre study was designed to compare the anti-emetic effectiveness of single oral doses of dolasetron mesilate with the approved, oral multiple-dose ondansetron regimen in cancer patients receiving moderately emetogenic chemotherapy. The ondansetron dosing regimen (8 mg, total dose of 24–32 mg) was chosen based on the results of several randomised and open-label studies for the control of emesis and nausea after moderately emetogenic chemotherapy [23–26]. Although a single, prechemotherapy dose of ondansetron has been studied, results among studies have been inconsistent [27]. Because of the excellent anti-emetic efficacy of single intravenous dolasetron mesilate doses and preliminary data with single oral doses, this study was conducted to compare single oral doses of dolasetron mesilate with the approved oral multiple-dose ondansetron regimen. Because more severe emetic responses have been observed in females and in patients who have had prior chemotherapy [28, 29], patients in this study were stratified according to gender and prior exposure to chemotherapy before randomisation.

PATIENTS AND METHODS

This randomised, multicentre, double-blind, European study compared the anti-emetic efficacy of four single oral doses of dolasetron mesilate (25, 50, 100 or 200 mg) with the standard, approved, multidose regimen of oral ondansetron (3 or 4 × 8 mg doses) in cancer patients scheduled to receive moderately emetogenic chemotherapy. Patients who qualified for the study received one of the five anti-emetic treatment regimens and were monitored for 24 h following chemotherapy to assess treatment efficacy, safety and tolerability.

Qualifying patients were stratified at entry by gender and by history of previous chemotherapy (naive, non-naive). Study entry was restricted to those patients who met the following entrance criteria: males or non-pregnant females ≥18 years of age; histologically confirmed malignant disease; Karnofsky performance status of ≥50%; scheduled to receive chemotherapy with moderately emetogenic drugs including carboplatin (≥300 mg/m^2), cyclophosphamide (≥600 mg/m^2 as combination therapy), doxorubicin (≥40 mg/m^2 as a single agent, ≥25 mg/m^2 as combination therapy), epirubicin (≥75 mg/m^2 as a single agent, ≥50 mg/m^2 as combination therapy), dacarbazine (≥350 to <500 mg/m^2), mustine (≥6 mg/m^2), or ifosfamide (≥1.8 g/m^2); and clinical laboratory tests within normal ranges considering the extent of malignant disease. Patients were also required to remain in the hospital for 4 to 8 h after the start of chemotherapy and return to the hospital or designated clinic after 24–36 h for final evaluations. All patients signed a written statement of informed consent prior to initiation of any study-related procedures.

Patients were excluded from the study for any of the following reasons: history of congestive heart failure; the presence of significant hepatic, neurological or psychiatric disease excluding alcoholism; vomiting or nausea (Southwest Oncology Group [SWOG] grade 2–4) during the 24 h prior to receiving chemotherapy; vomiting resulting from any organic aetiology; cerebral metastases that impaired communication or induced emesis; or, treatment with radiotherapy within 7 days, treatment with other anti-emetic drugs (e.g. other 5-HT$_3$ antagonists, trimethobenzamide, tricyclic antidepressants, droperidol, diphenhydramine, glucocorticoids) within 24 h, treatment with anticancer drugs within 72 h, or treatment with any investigational compound within 21 days of the scheduled chemotherapy. In addition, any patient who received concomitant medications (for reasons other than control of nausea and emesis) that possessed any anti-emetic activity within 24 h before or after chemotherapy (e.g. phenothiazines, corticosteroids) was excluded from efficacy analyses, but not from safety analyses.

Drug dosing and administration

Patients who met entry criteria were stratified according to gender and prior chemotherapy status and then randomised to receive one of the five drug treatment regimens. Blinding was maintained by dosing with identical numbers of tablets and capsules (active agent plus placebo for the comparative agent) at each scheduled dosing time throughout the study. Dolasetron mesilate (or matching placebo for ondansetron) was administered as tablets of differing sizes for each single oral dose of 25, 50, 100 or 200 mg. The single dolasetron mesilate dose was administered 1 h prior to the initiation of moderately emetogenic chemotherapy. Multiple doses of ondansetron (8 mg × 3 or 8 mg × 4) capsules, or matching placebo for patients randomised to dolasetron, were administered 1.5 h before chemotherapy and 6.5, 14.5 and 22.5 h after the start of chemotherapy (total dose = 32 mg). At four

centres in Italy, investigators requested the elimination of the last dose of ondansetron at 22.5 h, resulting in a total ondansetron dosage of 24 mg in a minority of patients. Escape anti-emetic medication could be given if the patient had experienced three or more emetic episodes or if the patient or physician requested such medication during the 24 h study period.

Efficacy evaluations

The number and timing of emetic episodes were recorded during the 24 h following chemotherapy. The primary determinant of anti-emetic efficacy was the proportion of complete responders in each treatment/dosage group and stratum. A complete response was defined as no emetic episodes and no escape anti-emetic medication within the 24 h postchemotherapy observation period. A major response was defined as one or two emetic episodes and no request for or use of escape anti-emetic medication. Patients were considered treatment failures (no response) if they had more than two emetic episodes within the 24 h observation period, received escape anti-emetic medication during this time, or did not have study data for at least 23.5 h after the start of chemotherapy.

Secondary efficacy parameters included the proportion of complete plus major responders in each treatment/dosage group and stratum and the time to the first emetic episode or use of escape anti-emetic medication. In addition, patients assessed the severity of nausea on a 100 mm visual analogue scale (VAS) with baseline evaluations made 1.5 h before chemotherapy (just prior to first dose of study drug) and 24 h following the start of chemotherapy. Nausea was evaluated according to a VAS scale of 0 mm (no nausea) to 100 mm (nausea as bad as it can be). Investigators also assessed the patients' most severe episode of nausea during the 0–8 h and 8–24 h postchemotherapy intervals on a scale of 0–4 (none, mild, moderate, severe nausea); the maximum of these two scores was analysed statistically. Further, patients completed a 100 mm VAS measuring their overall satisfaction with the anti-emetic treatment 24 h after the start of chemotherapy; 0 mm represented 'not satisfied' and 100 mm represented 'completely satisfied'. Treatment efficacy was also analysed by patient subgroup (e.g. age, gender, previous history of chemotherapy, use of steroids, narcotics, or benzodiazepines and type of chemotherapeutic regimen).

Safety evaluations

Safety was assessed throughout the study by means of adverse event reports and pre- and post-treatment vital signs, ECGs (at baseline and 24 h), physical examinations, and clinical laboratory tests (haematology, blood chemistry, urinalysis). Pretreatment (baseline) assessments were conducted during the 3 days prior to scheduled chemotherapy. These included a medical history, physical examination, clinical laboratory tests (haematology, blood chemistry, urinalysis), a 12-lead ECG, and measurements of vital signs. Adverse event reports were solicited throughout the 24 h postchemotherapy monitoring period. Vital signs were obtained every 30 min for the 1.5 h prior to the start of chemotherapy and 0.5, 1, 4, 8 and 24 h after chemotherapy.

Statistical methods

The sample size for this study (approximately 75 patients per treatment group) was chosen in order to achieve sufficient statistical power to detect a 25% difference in complete response rates between treatment groups. This sample size was also adequate to detect dose-related trends in complete response rates (using a logistic regression model) over the range of dolasetron mesilate doses tested (25–200 mg).

Baseline characteristics for the intent-to-treat patient population were assessed by a three-way analysis of variance (ANOVA) or logistic regression. Efficacy endpoints were analysed using logistic regression with a test for linear trend in the proportion of complete/major responders; no adjustments for multiple comparisons were made. Tests for interactions between investigator or patient stratum and linear dose response were accomplished using logistic regression, the residual chi-square test and the Mantel–Haenszel test. Ninety-five per cent confidence intervals for the odds ratios of dolasetron mesilate doses versus ondansetron were constructed using a primary logistic regression model. An assumption was made that the placebo response rate for the types of chemotherapeutic agents used in this study would be no more than 30%. Secondary endpoints were analysed as follows: the time to first emetic episode using the Cox regression model; nausea VAS and patient satisfaction ratings by ANOVA and logistic regression; and, investigators' evaluation of nausea severity using a Mantel–Haenszel non-zero correlation test controlling for stratum. Safety variables were tested by means of a three-way ANOVA; signs of linear trends were explored using logistic regression models.

RESULTS

Patient demographics and disposition

Overall, 399 patients at 26 European centres qualified for randomisation and were treated with study medications. A total of 316 patients received a single oral dose of dolasetron mesilate and 83 patients received multiple, 8 mg doses of ondansetron; 21 patients received a total of 24 mg of ondansetron and 62 patients received a total of 32 mg of ondansetron. However, 1 patient was randomised and received study drug, but did not subsequently receive the scheduled chemotherapy. As a result, the intent-to-treat efficacy analysis consisted of 398 patients, while the safety assessments included all 399 randomised patients.

Patient demographic characteristics were similar across all five treatment groups at baseline (Table 1). The overall population was predominantly female (61.2%), and the mean age was 53.2 years. Breast cancer was the most frequent primary neoplasm (40.1% of patients) followed by lung cancer (20.6% of patients). The mean Karnofsky status was 91.4% (median = 100%) and 53.6% of patients had received previous chemotherapy. The most frequently used chemotherapeutic agents during the study were cyclophosphamide (113 of 399, 28.4% of patients), doxorubicin (92 of 399, 23.1%), and carboplatin (82 of 399, 20.6%); 27.6% of patients received a platinum-based form of chemotherapy, alone or in combination with other agents. Multiple, moderately emetogenic, non-platinum agents were given to 37.2% of the patients. Regardless of whether chemotherapy regimens were platinum-containing or not, all regimens were administered at moderately emetogenic levels. No statistically significant imbalances occurred among the treatment groups for the type of primary chemotherapy or concomitant cytotoxic agents.

Efficacy

The 315 patients in the intent-to-treat population who received dolasetron had an overall complete response rate of

Table 1. Baseline characteristics for the intent-to-treat patient population

Variable	Treatment group: Dolasetron mesilate 25 mg ($n = 80$)	50 mg ($n = 80$)	100 mg ($n = 76$)	200 mg ($n = 80$)	Ondansetron ($n = 83$)	All patients ($n = 399$)
Gender (%)						
Male	41.3	38.8	43.4	38.8	32.5	38.8
Female	58.8	61.3	56.6	61.3	67.5	61.2
Mean age (years)	53.1	50.9	53.2	54.2	54.4	53.2
S.D.	14.6	13.0	13.4	11.8	12.1	13.0
Mean Karnofsky status (%)	89.8	92.4	91.8	90.8	92.2	91.4
Standard deviation	12.4	9.8	10.2	11.5	10.3	10.9
Primary chemotherapy (%)						
Carboplatin	26.3	17.7	15.8	22.5	20.5	20.6
Cyclophosphamide	27.5	31.6	25.0	27.5	30.1	28.4
Doxorubicin	23.8	19.0	22.4	26.3	24.1	23.1
Epirubicin	7.5	11.4	11.8	7.5	9.6	9.5
Other	15.0	20.0	25.0	16.3	15.7	18.3

57.7% (182 of 315). As shown in Table 2, there was a statistically significant ($P < 0.0001$) trend in the proportion of complete responders with increasing dolasetron mesilate dose that was consistent for all investigative sites. Patients treated with 200 mg dolasetron mesilate had significantly ($P \leq 0.0188$) higher complete response rates than those who received 25, 50 or 100 mg of dolasetron mesilate. Further, there were no statistically significant differences among the 25, 50 or 100 mg dolasetron mesilate dosage groups for proportion of complete responses. The high rate of complete responses observed with 200 mg of dolasetron mesilate (61 of 80, 76.3%) was comparable with that observed for ondansetron (60 of 83, 72.3%) (Table 2). Ondansetron produced a significantly ($P \leq 0.0011$) higher proportion of complete responses compared with the lower doses of dolasetron mesilate (25 or 50 mg). Similar results among dolasetron mesilate dosage groups, and between dolasetron and ondansetron were observed for complete plus major responses.

As shown in Table 2, a statistically significant ($P = 0.0001$) linear trend was apparent for the time to the first emetic episode (or first use of escape anti-emetic medication) for the four dolasetron mesilate doses. The median interval varied from 19.58 h for the 25 mg dolasetron mesilate group to >24 h for the 100 and 200 mg dose group. The median time to first emetic episode for the ondansetron group was also >24 h.

A significant ($P = 0.0001$) linear trend in nausea VAS changes from baseline with increasing dolasetron mesilate dose was evident (Table 2). The median change from baseline in nausea VAS scores was significantly ($P \leq 0.0019$) lower in the 200 mg dolasetron mesilate group compared with the other three dolasetron mesilate dosage groups and significantly ($P = 0.0061$) lower than the ondansetron group at 24 h postchemotherapy. The investigators' assessments of patients' most severe episode of nausea supported the patients' VAS evaluations, although differences between 200 mg dolasetron mesilate and ondansetron were not statistically significant. Investigators reported that no nausea was present for 45.6, 36.7, 53.3 and 69.6% of patients who received 25, 50, 100 and 200 mg of dolasetron mesilate, respectively, and for 57.3% of ondansetron-treated patients. Patient satisfaction with dolasetron treatment increased with increasing dose ($P < 0.0001$). Median patient satisfaction ratings ranged from 54 mm (25 mg) to 99 mm (200 mg) in the dolasetron mesilate groups and the median rating for ondansetron was 98 mm.

Table 2. Anti-emetic efficacy of single oral doses of dolasetron mesilate and multiple-dose ondansetron

Response	Treatment group: Dolasetron mesilate 25 mg ($n = 80$)	50 mg ($n = 79$)	100 mg ($n = 76$)	200 mg ($n = 80$)	Ondansetron ($n = 83$)
Complete response* (%)	45.0	49.4	60.5	76.3†	72.3‡
Complete + major response* (%)	57.5	59.5	72.4§	85.0†	78.3‡
No response (%)	42.5	40.5	27.6	15.0	21.7
Median time to first emetic episode (h)*	19.58	21.75	>24.00	>24.00	>24.00
Patient VAS evaluation of nausea (median change from baseline at 24 h)*	29.0	31.0	3.5	0.0‖	3.0

*Statistically significant linear trend for dolasetron mesilate dose ($P \leq 0.0001$). †Significantly different ($P \leq 0.0188$) from dolasetron mesilate 25, 50 and 100 mg groups. ‡Significantly different ($P < 0.0011$) from dolasetron mesilate 25 and 50 mg groups. §Significantly different ($P = 0.0454$) from dolasetron mesilate 25 mg group. ‖Significantly different ($P = 0.0061$) from ondansetron group. Significantly different ($P \leq 0.0019$) from dolasetron mesilate 25, 50 and 100 mg groups.

Table 3. Subgroup analysis of anti-emetic efficacy of single oral doses of dolasetron mesilate and multiple-dose ondansetron

Complete response by subgroups	Treatment group: Dolasetron mesilate 25 mg ($n = 80$)	50 mg ($n = 79$)	100 mg ($n = 76$)	200 mg ($n = 80$)	Ondansetron ($n = 83$)
Age*§					
<65 years	43.9	47.8	55.7	70.0	70.3
≥65 years	50.0	58.3	80.0	95.0	78.9
Gender*†					
Male	54.5	61.3	72.7	80.6	77.8
Female	38.3	41.7	51.2	73.5	69.6
Prior chemotherapy*‡					
No	39.5	60.5	56.4	81.8	78.4
Yes	50.0	39.0	64.9	72.3	67.4

*Statistically significant linear trend for dolasetron mesilate ($P < 0.0001$). †Males versus females receiving dolasetron ($P = 0.0015$). ‡Chemotherapy naive versus non-naive patients receiving dolasetron ($P = 0.0212$). §Patients <65 years versus ≥65 years receiving dolasetron ($P = 0.0078$).

Subgroup analyses

Subgroup analyses revealed differences in the complete response rates according to age, gender and previous exposure to chemotherapy. Overall, complete response rates (Table 3) were significantly ($P = 0.0015$) higher in males than in females, in patients who were naive to chemotherapy compared with those who received previous chemotherapy ($P = 0.0212$), and in patients ≥65 years of age relative to those younger than 65 ($P = 0.0078$). As shown in Table 3, linear trends with dolasetron mesilate dose were also statistically significant for the subgroup analyses ($P < 0.0001$). No statistically significant subgroup differences were observed with respect to the proportion of complete responders for the following variables: use of narcotics, use of steroids, use of benzodiazepines, or type of chemotherapeutic regimen employed during the study.

Safety

The safety profiles for dolasetron and ondansetron in this study were comparable. The majority of adverse events were mild or moderate in intensity. As shown in Table 4, the overall incidence of adverse events was 25.0, 37.5, 39.5, 33.8 and 36.1% for the 25, 50, 100, 200 mg dolasetron mesilate groups, and ondansetron group, respectively. There was no statistically significant linear trend with dolasetron mesilate dose for overall adverse events.

The most commonly reported adverse event for all treatment groups was mild-to-moderate headache, which occurred in 11.3, 8.8, 19.7 and 18.8% of patients who received 25, 50, 100 and 200 mg of dolasetron mesilate, respectively, and 14.5% of patients given ondansetron. No significant trend with dose was apparent for the four dolasetron mesilate dosage groups with respect to the frequency of headaches. All other adverse events were reported sporadically by less than 5% of patients. Three deaths occurred at least 4 days after drug administration (two with dolasetron, one with ondansetron) and were all attributed to progression of the patients' cancers. There were no clinically important changes in vital signs or laboratory parameters observed during the study.

DISCUSSION

The results of this large, multicentre, European study demonstrated that a single 200 mg oral dose of dolasetron mesilate salt (148 mg dolasetron mesilate base) was at least therapeutically equivalent to the standard oral regimen of ondansetron for the prevention of emesis (based on complete response), and was significantly superior to ondansetron with respect to control of nausea after moderately emetogenic chemotherapy.

Table 4. Overall adverse events reported by ≥3% of patients

Adverse event	Treatment group: Dolasetron mesilate 25 mg ($n = 80$)	50 mg ($n = 80$)	100 mg ($n = 76$)	200 mg ($n = 80$)	Ondansetron ($n = 83$)
Overall	20 (25.0)	30 (37.5)	30 (39.5)	27 (33.8)	30 (36.1)
Headache	9 (11.3)	7 (8.8)	15 (19.7)	15 (18.8)	12 (14.5)
Dizziness	0	2 (2.5)	3 (3.9)	1 (1.3)	0
Diarrhoea	0	3 (3.8)	2 (2.6)	4 (5.0)	1 (1.2)
Constipation	0	3 (3.8)	1 (1.3)	1 (1.3)	0
Drowsiness	0	2 (2.5)	3 (3.9)	3 (3.8)	2 (2.4)
Weakness	1 (1.3)	3 (3.8)	1 (1.3)	0	1 (1.2)
Fatigue	0	0	2 (2.6)	1 (1.3)	3 (3.6)
Fever	1 (1.3)	1 (1.3)	0	0	4 (4.8)

All values represent number (and percentage) of patients experiencing an event; 1 patient may have had more than one event.

Complete responses achieved by patients given 200 mg of dolasetron mesilate were numerically higher than, but statistically similar to ondansetron (76 versus 72%, respectively) as were complete plus major responders (85 versus 78%, respectively). A statistically significant anti-emetic dose–response relationship was observed over the entire dolasetron mesilate dosage range tested (25 to 200 mg). Dolasetron mesilate 200 mg was superior to the other single oral doses of dolasetron mesilate (25, 50, 100 mg dolasetron mesilate salt, expressed as 18.5, 37 and 74 mg of dolasetron base, respectively) for all efficacy parameters. Therapeutic equivalence bewtween 200 mg of dolasetron mesilate and ondansetron was apparent for all secondary efficacy parameters including time to first emetic episode, use of escape anti-emetic medication, patient and investigator nausea assessments, and patient satisfaction with treatments.

The anti-emetic efficacy observed with single oral doses of dolasetron mesilate is similar to results obtained in prior dose ranging studies when given intravenously [14–17] and orally [22], and in phase II, randomised, double-blind studies comparing different intravenous dolasetron mesilate doses and regimens [19–21]. Results with the oral, multiple-dose ondansetron regimen in our study paralleled those found in previous studies, particularly when ondansetron was used for the first day of treatment [2, 23, 25, 27, 30–32].

Subgroup analyses also compared favourably to data reported in other studies with anti-emetic agents [4, 5, 32]. That is, complete response rates were higher in males than in females, in older patients rather than younger patients, and in chemotherapy-naive patients compared with those who have had prior chemotherapy. The differences observed between the subgroups in this study were relatively small ($\leq$15%) for the variables of gender and chemotherapy history, but were nonetheless statistically significant. Because patients who have had prior chemotherapy and poor control of nausea and emesis are likely to be less responsive to subsequent anti-emetic therapy, it is important that agents have substantial initial efficacy for the prevention of nausea and vomiting in the first 24 h. Our study has confirmed the value of single dose dolasetron for the prevention and control of chemotherapy-induced nausea and emesis during the first 24 h after moderately emetogenic chemotherapy.

Both dolasetron and ondansetron were well tolerated in this study. The incidence of adverse events and changes in clinical laboratory variables were consistent with what one might expect in severely ill cancer patients. Adverse events were generally mild in intensity and were similar across all treatment groups. Headache was most commonly observed and was consistent with the class of 5-HT_3 antagonists [4, 5]. Other commonly reported adverse events were gastrointenstinal symptoms, and relatively few single events were reported by more than 3% of patients in any treatment group. Importantly, no dose-dependent trend was seen for the frequency of the most commonly reported adverse events (headache, gastrointestinal effects). A previous study in patients receiving moderately emetogenic chemotherapy and dolasetron reported some asymptomatic treatment-emergent changes in ECG parameters that were not clinically significant [15]. ECGs in the present study were obtained at a time (24 h after chemotherapy) when plasma concentrations of dolasetron and its reduced metabolite were low. Therefore, the study design did not adequately permit direct assessment of ECG changes. No clinically significant ECG changes were observed in this study, and no clinically evident cardiovascular events that would be expected to occur from these ECG alterations have been reported in this or other dolasetron studies to date. Both dolasetron and ondansetron lack the extrapyramidal effects associated with the use of traditional anti-emetics such as metoclopramide.

Confirmation of a drug's efficacy and tolerability when given orally is important, because oral forms are more convenient, less invasive, less expensive, and are generally more acceptable to the patient than intravenous dosage forms [2]. Furthermore, because patient compliance decreases as the complexity of the dosing regimen increases, a need to dose more than once daily can result in significant loss of therapeutic efficacy as a result of non-compliance [33–35]. This is especially true with orally administered agents in an outpatient setting. Therefore, the finding that a single oral dose of dolasetron mesilate provided therapeutically equivalent anti-emetic efficacy compared with the approved, standard, multiple-dose oral ondansetron regimen will have important economic and compliance implications for cancer patients.

In summary, this large, multicentre, European comparative study of the anti-emetic efficacy of orally administered dolasetron mesilate and ondansetron clearly shows that a single, oral 200 mg dolasetron mesilate dose is therapeutically equivalent to a standard, multiple-dose regimen of oral ondansetron (8 mg × 3 or 4 doses) with respect to prevention of emesis in cancer patients receiving moderately emetogenic chemotherapy. Both agents were well tolerated and without significant or serious adverse effects. The advantages of single-dose oral dolasetron mesilate therapy make this agent an important and valuable therapeutic addition for the prevention and control of chemotherapy-induced nausea and vomiting.

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