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ORIGINAL ARTICLE

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A randomized, double-blind comparison of single-dose and divided multiple-dose dolasetron for cisplatin-induced emesis

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Abstract *Purpose:* Intravenous dolasetron has been shown to be an effective antiemetic agent in patients receiving high-dose cisplatin-containing chemotherapy. Previous studies have suggested that 1.8 mg/kg is an optimal dose for achieving control of emesis and nausea. The objective of this study was to compare the efficacy and safety of a single intravenous (IV) dose of dolasetron with an equal divided multiple dose. *Methods:* In this randomized, double-blind, parallel-group, multicenter study, the efficacy and safety of a single 1.8-mg/kg dose of dolasetron given 30 min prior to high-dose cisplatin (≥ 80 mg/m^2) chemotherapy was compared with the same total amount of dolasetron administered in three separate doses (0.6 mg/kg each) over a 12-h interval commencing 30 min prior to beginning chemotherapy and ending 11.5 h later. Antiemetic efficacy, safety, and tolerability were compared in 55 patients with various malignancies during the 24 h following the initiation of chemotherapy. The number of emetic episodes was the primary efficacy parameter. *Results:* A single IV dose of dolasetron was generally more effective than a multiple-dose regimen in all measures of efficacy. There was a larger proportion of complete responders in the single-dose group compared with the multiple-dose group (48% vs 23%), although this difference did not reach statistical significance. Compared with the multiple-dose group, patients who received a single dose of dolasetron had a significantly ($P = 0.034$) longer median time to the first emetic episode (10.1 h vs > 24 h, respectively). Overall, 53% of patients had either a complete response or a major response to dolasetron, and only 40% of the total patient population received escape antiemetic medication in the 24 h after cisplatin administration. Except for headache, adverse events were similar with both regimens and were generally of mild or moderate intensity; no serious adverse events occurred. Neither dolasetron treatment regimen was associated with any clinically important events, trends in laboratory variables, or differences in safety profile. *Conclusions:* single-dose dolasetron was well tolerated and effectively controlled emesis and nausea in patients who received highly emetogenic, high-dose cisplatin chemotherapy. The greater antiemetic efficacy of a single prophylactic dose of dolasetron offers both convenience and potential cost savings, compared with a multiple-dose schedule of administration.

Key words Dolasetron · Antiemetic · 5-HT$_3$ antagonist

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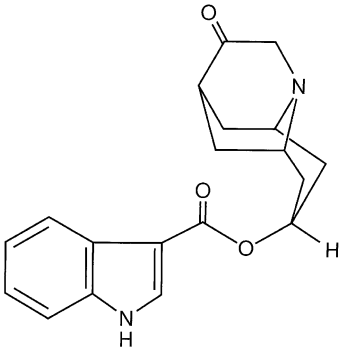
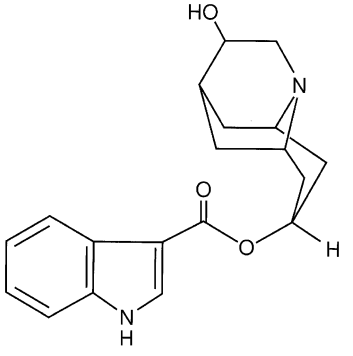
Introduction

Although the introduction of the newer 5-HT$_3$ antagonists into clinical practice has heralded a new era in antiemetic control for patients receiving chemotherapy, a number of key issues, such as optimal dose and dosing regimen, remain to be resolved [8, 10]. Furthermore, the reported clinical effectiveness of these drugs may vary with dose, chemotherapeutic regimen, and a number of demographic factors [1, 8, 10]. Multiple-dose schedules of the presently available 5-HT$_3$ antagonists have not been shown to be superior to a single



Dolasetron



Reduced Metabolite

Fig. 1 Chemical structures of dolasetron (MDL 73,147) and its major metabolite (MDL 74,156)

prophylactic dose [17, 20, 22]. In addition, these drugs are effective in most patients and generally are safe and well tolerated over a wide dose range.

Dolasetron is a novel pseudopelletierine-derivative 5-HT_3 antagonist (Fig. 1) [3, 6, 7, 19]. Dolasetron is rapidly and extensively metabolized to a more potent ($>$ 50-fold vs the parent drug) and selective compound (MDL 74,156) [3] with a longer half-life than the parent drug (Fig. 1) [4]. Pharmacokinetic studies have suggested that neither dolasetron nor its active metabolite are likely to accumulate appreciably with repeated dosing [12].

Intravenous (IV) dolasetron has been well tolerated in normal volunteers [9, 13], and investigations in cancer patients undergoing highly and moderately emetogenic chemotherapy have demonstrated dose-dependent efficacy for doses ranging from 10 mg to 50 mg [5, 16, 18]. These and other studies [2, 14, 15, 21] have suggested that doses higher than 0.3 mg/kg might be necessary for optimum antiemetic efficacy. A study by Hesketh et al. [11] in cancer patients who received moderately emetogenic chemotherapy, demonstrated that 1.8 mg/kg of dolasetron has optimal efficacy and is well tolerated for the prevention of emesis and nausea. Therefore, a determination was made based on these studies that an intravenous (IV) dolasetron dose of 1.8 mg/kg represented a reasonable estimate of a fully effective dose at the time this study was developed.

This study was designed to evaluate the relative efficacy and safety of a single-dose versus a divided multiple-dose regimen. Based on prior studies demonstrating dose-dependent antiemetic efficacy, a single 1.8-mg/kg dose given 30 min prior to high-dose cisplatin ($\geq$ 80 mg/m^2) chemotherapy was compared with the same total amount of dolasetron administered in three separate doses (0.6 mg/kg each) over a 12-h period commencing 30 min prior to beginning chemotherapy and ending 11.5 h later.

Materials and methods

Study design

This was a randomized, double-blind, parallel-group, multicenter study designed to evaluate the antiemetic efficacy, safety, and tolerability of two IV dosing regimens of dolasetron in cancer patients undergoing chemotherapy with high-dose cisplatin ($\geq$ 80 mg/m^2). One group of patients received a single IV dose of dolasetron (1.8 mg/kg) before commencing chemotherapy, while the second group received a total of 1.8 mg/kg in three equally divided doses. Patients were evaluated for a 24-h period after the initiation of chemotherapy. The efficacy of each dolasetron regimen was assessed by recording the timing and number of postchemotherapy episodes of emesis and/or retching, the patients' rating of nausea on a 100-mm visual analogue scale (VAS), and the timing and use of escape antiemetic medication. Safety was evaluated by monitoring adverse event reports and pretreatment and posttreatment vital signs and clinical laboratory values. Southwest Oncology Group (SWOG) toxicity criteria were used throughout the study.

Patient population

The study enrolled patients of either gender who were at least 18 years of age and had histologically confirmed malignant disease that was to be treated with high-dose cisplatin ($\geq$ 80 mg/m^2) for the first time. Patients were required to have a Karnofsky performance status of $>$ 50% and to fulfill the following clinical laboratory criteria for the administration of cisplatin: WBC $\geq$ 3000/ µl, platelets $\geq$ 100 000/ µl, total bilirubin $\leq$ 2.5 mg/dl, AST/ALT within $\pm$ 2 times normal limits, and serum creatinine $\leq$ 1.5 mg/l.

Patients were excluded from the study if they had undergone previous treatment with cisplatin or dolasetron; had received any investigational agent within the past 21 days; had a history of recent vomiting due to any organic etiology; had vomiting or SWOG grade 2–4 nausea within 24 h before chemotherapy; had experienced SWOG grade 2–4 nausea or vomiting after previous noncisplatin chemotherapy; or had used any other drugs with antiemetic activity within 24 h of the start of chemotherapy. Patients with a known seizure disorder or a history of significant neurologic or psychiatric illness (with the exception of alcoholism) also were excluded. Females of childbearing potential were excluded if they were pregnant or were not using adequate contraception.

The study protocol was approved by the respective Institutional Review Boards at the four clinical centers. Each patient gave written informed consent before entering the study.

Drug dosing and administration

Cisplatin (≥ 80 mg/m^2) was infused over a period that was not to exceed 3 h. Dolasetron (10 mg/ml) was supplied as a sterile aqueous isotonic IV solution in 10-ml ampoules. Before administration, the appropriate dose of dolasetron was diluted to a total volume of 50–100 ml with sterile isotonic saline. The dose was administered by IV infusion over 10 min. Two dose regimens were evaluated: a single IV dose of 1.8 mg/kg, given 30 min before the start of chemotherapy, plus placebo infusions at 5.5 and 11.5 h after initiation of chemotherapy; or three IV doses of 0.6 mg/kg each, administered 30 min prior to chemotherapy and at 5.5 and 11.5 h after initiation of chemotherapy.

Efficacy evaluations

The efficacy of dolasetron was assessed by examining the number of vomiting and/or retching episodes, the elapsed time until the first vomiting/retching episode, the severity of nausea, the timing and use of escape antiemetic medication, and the patients' and investigators' global assessments of the effectiveness of antiemetic therapy with dolasetron. The assessment period was the 24-h period following initiation of chemotherapy.

An emetic episode was defined as one instance of vomiting or any number of retches within a 5-min period. Responses were defined as: *complete* (no emetic episodes and no escape medication in 24 h), *major* (one or two emetic episodes and no escape medication in 24 h), and *no response* (more than two emetic episodes and/or the need for escape medication in 24 h). Severity of nausea was rated on a VAS from 0 mm (no nausea) to 100 mm (nausea as bad as it can be). Patients' assessments of nausea were obtained 45 min before chemotherapy (15 min before the prechemotherapy dolasetron dose), immediately prior to chemotherapy (hour 0), and 24 h after the start of chemotherapy. The 24-h nausea rating evaluated the patients' average nausea for the 24-h period after the start of cisplatin. Patient and investigator global evaluations were completed 24 h after the start of chemotherapy. Escape medication was given to any patient who requested it and to any patient who experienced more than three emetic episodes. The type of escape medication used was at the discretion of each treating physician.

Safety evaluations

Adverse event reports were solicited throughout the 24-h post chemotherapy period. Events were classified as to intensity, seriousness, and possible relationship to dolasetron administration. Vital signs were obtained at 45 min before initiation of chemotherapy and at selected intervals throughout the postchemotherapy period, and clinical laboratory evaluations (hematology, urinalysis, and blood chemistry) were performed within 72 h of beginning chemotherapy, 15 min before dolasetron dosing, and at the end of the 24-h postchemotherapy period. A 12-lead electrocardiogram (ECG) was obtained pretreatment.

Statistical analysis

A comparison of the proportions of complete and major responders in each dolasetron treatment group was accomplished using the Mantel-Haenszel test. Differences in VAS scores between treatment groups were analyzed using Student's *t*-test. The duration of antiemetic effect (time to first emetic episode) or the time to treatment failure (time to first administration of escape medication) was compared between groups by means of the Cox Proportional Hazards model.

Table 1 Patient characteristics. Values for age, height and weight are means $\pm$ standard deviation

Variable	Dolasetron dosing regimen		
	Single IV dose (1.8 mg/kg) ($n = 25$)	Multiple IV doses (0.6 mg/kg $\times$ 3) ($n = 30$)	Total ($n = 55$)
Mean age (years)	58.2 $\pm$ 8.1	58.6 $\pm$ 11.2	58.4 $\pm$ 9.8
Mean height (cm)	172.9 $\pm$ 10.6	171.7 $\pm$ 9.1	172.2 $\pm$ 9.7
Mean weight (kg)	74.3 $\pm$ 17.2	77.9 $\pm$ 16.1	76.3 $\pm$ 16.5
Gender (%)			
Male	68	63	65
Female	32	37	35
Race (%)			
Caucasian	96	93	95
Black	4	3	3
Other	0	3	2
Median Karnofsky performance			
Status (%)	90	90	90
Range	70–100	60–100	60–100
Previous chemotherapy (%)			
Yes	16	20	18
No	84	80	82

A treatment failure was defined as more than three emetic episodes, although four patients in each dosing group requested escape medication before three emetic episodes. For the purposes of analysis, any patient who requested escape medication was considered a treatment failure.

Results

Patient demographics

A total of 55 patients were enrolled at four clinical centers; all patients were included in the safety and efficacy analyses. Only minor protocol violations occurred during the study, and none was considered likely to influence the interpretation of the study results. Table 1 summarizes the demographic characteristics of the study population. The sample was predominantly male (65%) and Caucasian (95%). Mean Karnofsky performance status was 89.5%. Lung cancer was the most common form of malignancy represented (42% of patients overall). The two treatment groups were equivalent across most demographic variables, although some minor imbalances were noted between the groups with respect to prior medical history. There also were no differences between the groups with respect to prior history of heavy alcohol intake.

Overall, the mean cisplatin dose was 94.8 mg/m^2 infused over a mean of 1.27 h; there were no differences in cisplatin dosing between the dolasetron groups. Antineoplastic agents used in addition to cisplatin included etoposide, 5-fluorouracil, ifosfamide, cytarabine, doxorubicin, dacarbazine, vinblastine, and cyclophosphamide. There were no significant imbalances

Table 2 Efficacy of two dolasetron dosing regimens on cisplatin-induced emesis

Variable	Dolasetron dosing regimen		
	Single IV dose (1.8 mg/kg) ($n = 25$)	Multiple IV doses (0.6 mg/kg × 3) ($n = 30$)	Total ($n = 55$)
Responders[a] (%)			
Complete	48	23	35
Major	16	20	18
No response	36	57	47
Median time to first emetic episode (h)	> 24	10.1	20.2
Median number of emetic episodes	0	2	1
Patients who received escape therapy[b] (%)	32	47	40
Median time to escape therapy (h)	> 24	> 24	> 24

[a]Any patient who requested escape therapy, regardless of the number of preceding emetic episodes, was considered a nonresponder for the purposes of this analysis
[b]Escape therapy was to be given after the patient had experienced more than three emetic episodes or when the patient requested such therapy

Table 3 Efficacy of two dolasetron dosing regimens on cisplatin-induced nausea

	Dolasetron dosing regimen		
	Single IV dose (1.8 mg/kg) ($n = 25$)	Multiple IV doses (0.6 mg/kg × 3) ($n = 30$)	Total ($n = 55$)
Nausea rating on 0–100 mm VAS (median, range)			
Baseline[a]	0 (0–5.0)	0 (0–10.0)	0 (0–10.0)
Time[b]	0 (0–5.0)	0 (0–9.0)	(0 (0–9.0)
Time ∅ + 24 h	9.0 (0–97.0)	44.5 (0–100.0)	22.0 (0–100.0)
Percent of patients with postchemotherapy VAS ≤ 10 mm	56	20	62
Median maximum change in VAS from baseline (mm)	8.0	43.5	22.0

[a]45 min before initiation of chemotherapy
[b]Initiation of cisplatin chemotherapy

between the two treatment groups with respect to prior administration of chemotherapy agents.

Efficacy

The effects of the two dolasetron dose regimens on the number of emetic episodes (responder vs nonresponder classification), the timing of those episodes, and the need for escape therapy are summarized in Table 2. The single-dose regimen was numerically more effective than the multiple-dose regimen for all measures of efficacy, but statistical superiority for single-dose dolasetron was only demonstrated for time to first emetic episode. There was a trend toward statistical significance between the regimens with a greater percentage of complete responders in the single-dose group compared with the multiple-dose group (no emetic episodes in 24 h, 48% vs 23%, respectively, $P = 0.065$). Patients who received the single-dose regimen also had a lower median number of emetic episodes (none vs two, respectively). One patient in the single-dose group had no emetic episodes over the first 24 h but requested escape medication due to nausea; therefore, this patient was considered a treatment failure for the primary efficacy analysis. Compared with the multiple-dose group, patients who received a single dose of dolasetron had a significantly ($P = 0.034$) longer median time to the first emetic episode (10.1 h vs > 24 h, respectively). In addition, the single-dose patients required or requested less escape therapy (32% vs 47%). Overall, 53% of patients had either a complete response or a major response to dolasetron, and only 40% of the total patient population received escape antiemetic medication in the 24 h after cisplatin administration.

Results obtained from VAS evaluations of cisplatin-induced nausea also favored the single-dose regimen of dolasetron (Table 3). With the single-dose regimen, 56% of patients reported having no nausea during the 24 h after the start of cisplatin, while only 20% of those in the divided multiple-dose group had no nausea during the same time period. Both the median 24-h VAS rating and the median maximum change from baseline were lower with the single-dose than with the multiple-dose regimen. The differences between treatment groups for these parameters were considerable, but none attained statistical significance. Patient and physician global evaluations of the efficacy of dolasetron therapy were qualitatively similar to the results of the objective measures summarized above: patients perceived the single-dose regimen as more efficacious than the multiple-dose regimen, with 80% of patients receiving the single dose reporting satisfaction with the treatment (i.e. 'satisfied' or 'very satisfied') compared with 57% of patients in the multiple-dose group.

Various subgroups of the patient population demonstrated differing degrees of response to the two dolasetron regimens. Male gender, age ≤ 65 years, and a history of heavy drinking were associated with greater effectiveness in the single-dose group. Neither Karnofsky performance status nor type of concomitant antineoplastic therapy appeared to be related to dolasetron efficacy. However, some of these observations were based on very small numbers of patients in each comparative group, and the possible clinical interpretation of such differences is necessarily limited.

Table 4 Adverse events Reported by at least two patients who received dolasetron. Values are the number (and percentage) of patients experiencing the event

	Dolasetron dosing regimen		
Adverse event	Single IV dose (1.8 mg/kg) ($n = 25$)	Multiple IV doses (0.6 mg/kg × 3) ($n = 30$)	Total ($n = 55$)
Headache	11 (44)	10 (33)	21 (38)
Diarrhea	6 (24)	6 (20)	12 (22)
Back pain	1 (4)	1 (3)	2 (4)
Chills	1 (4)	1 (3)	2 (4)
Shortness of breath	2 (8)	0	2 (4)
Increased appetite	2 (8)	0	2 (4)

Safety

Most of the adverse events reported during the study were mild or moderate in intensity. Two patients in the multiple-dose group experienced severe adverse events: one of these events (back pain secondary to metastatic disease) was judged unrelated to dolasetron administration, while the other (severe diarrhea) was attributed by the investigator to dolasetron. Table 4 lists the most frequently reported adverse events (those occurring in two or more patients in either treatment group). Headache (38%) and diarrhea (22%) occurred with equal frequency in both groups. Two patients in the single-dose group experienced moderate shortness of breath that was rated unrelated to study medication; both patients recovered fully after treatment. When considering the total incidence of adverse events (those reported by one or more patients), the incidence of central or peripheral nervous system events was greater with the single-dose (12/25, 48%) than with the multiple-dose regimen (11/30, 37%). In contrast, with respect to all reported gastrointestinal adverse events, they were more frequent with the multiple-dose (10/30, 33%) than with the single-dose regimen (6/25, 24%).

Occasional changes in vital signs and clinical laboratory results were observed throughout the study, but no trends were apparent for any variable. These alterations were unlikely to have been related to dolasetron treatment, given the patients' disease status and concurrent therapy with antineoplastic agents.

Discussion

This study demonstrated that a single IV dose of dolasetron was more effective and as well tolerated as an equal dose given as a divided-dose regimen in 55 cancer patients undergoing high-dose (≥ 80 mg/m^2) cisplatin chemotherapy for a variety of malignancies. Patients who received the single 1.8-mg/kg dolasetron dose exhibited a greater degree of control of emesis and nausea and less requirement for escape antiemetic medication than patients in the multiple-dose group. In addition, more patients who received the single-dose regimen expressed satisfaction with their assigned treatment than did patients in the multiple-dose group. The likelihood of the 0.6-mg/kg multiple-dose being more effective than the single 1.8-mg/kg dose is remote based on these results. The two dosing regimens were essentially indistinguishable with respect to the overall frequency of reported adverse events and have similar safety profiles.

The optimum dose and schedule of 5-HT$_3$ antagonist antiemetics, including dolasetron, remains to be determined. It is worth noting, however, that some studies with other 5-HT$_3$ antagonists (e.g. ondansetron, granisetron, tropisetron) have shown that there may not be an additional benefit to using multiple-dose regimens instead of single doses [17, 20, 22]. This may reflect some aspect of the mechanism of action of these compounds that is currently unappreciated. Clinical studies to determine the optimum dose of dolasetron are underway.

Cisplatin chemotherapy provides a good opportunity to evaluate the efficacy of antiemetic agents because of the intensity of the nausea and vomiting produced by this drug [8]. The efficacy exhibited by dolasetron in this study compares favorably with response rates reported for ondansetron, granisetron, and tropisetron under similar treatment parameters [10, 17, 20, 22]. The safety profile observed in our study was consistent with other 5-HT$_3$ antagonist antiemetics [17, 20, 22], with headache and diarrhea being the most frequent adverse events.

Single-dose administration of an antiemetic has potential advantages over a multiple-dose regimen with respect to cost, convenience of use, and flexibility for outpatient use. The results of this study show that the use of one prechemotherapy dose of dolasetron does not compromise efficacy, but rather provides greater efficacy than a divided multiple-dose regimen.

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