Support Care Cancer (1996) 4:141–146

ORIGINAL ARTICLE

Paul J. Hesketh
David R. Gandara
Ann M. Hesketh
Anna Facada
Edith A. Perez
Lauri M. Webber
Lorene A. Martin
Michael B. Cramer
William F. Hahne

Dose-ranging evaluation of the antiemetic efficacy of intravenous dolasetron in patients receiving chemotherapy with doxorubicin or cyclophosphamide

P.J. Hesketh, M.D. (✉)
A.M. Hesketh, R.N. · L.M. Webber, M.S.
Section of Medical Oncology,
St. Elizabeth's Medical Center,
736 Cambridge Street,
Boston, MA 02135, USA
Tel.: (617) 789–2317
Fax: (617) 789–2959

D.R. Gandara, M.D. · E.A. Perez, M.D.
UCD Cancer Center,
University of California,
Davis, 4501 X Street,
Sacramento, CA 95817, USA

A. Facada
Boston University Medical Center,
Section of Medical Oncology,
88 East Newton Street,
Boston, MA 02118, USA

L.A. Martin, M.S. · M.B. Cramer, Ph.D.
W.F. Hahne, M.D.
Marion Merrell Dow Inc.,
9300 Ward Parkway,
Kansas City, MO 64114, USA

Abstract Selective 5-HT_3 antagonists have proven to be safe and effective for the prevention of chemotherapy-induced nausea and vomiting. Dolasetron is a new highly selective addition to this class of antiemetics that has been shown to have significant antiemetic activity in patients receiving cisplatin-containing regimens. This pilot study was designed to evaluate the antiemetic efficacy of dolasetron in cancer patients receiving doxorubicin and/or cyclophosphamide. This study used an open-label, non-randomized design to evaluate the efficacy and safety of intravenous dolasetron in the prevention of emesis in patients receiving doxorubicin (25–75 mg/m^2) and/or cyclophosphamide (400–1200 mg/m^2). Sixty-nine patients received a single, intravenous dose of dolasetron over 15–20 min beginning 30 min prior to the start of chemotherapy. Dose levels of dolasetron studied were: 0.3, 0.6, 1.2, 1.8 and 2.4 mg/kg. Patients were monitored for emesis, nausea and adverse events for 24 h after the start of chemotherapy. Overall, 61% of patients experienced complete control of emesis. No significant trend towards increased antiemetic efficacy ($P=0.076$) or nausea control with increasing dolasetron dose was noted, although the power to detect significant differences was limited by the small number of patients on the 0.3-mg/kg and 2.4-mg/kg dose levels. Age, gender, and type of chemotherapy were significant predictors of complete antiemetic control. Adverse events were generally mild and included headache, chills, lightheadedness, fever, diarrhea, dizziness, and asymptomatic prolongation of ECG intervals. Intravenous dolasetron is safe and effective in the prevention of emesis induced by doxorubicin and/or cyclophosphamide.

Key words Dolasetron · Dose-ranging trial · Emesis · Nausea · Antiemetic

Introduction

The discovery that the type 3 5-hydroxytryptamine (5-HT_3) receptor plays a role in the pathogenesis of chemotherapy-induced emesis has led to the development of a new class of antiemetic agents, the selective 5-HT_3 antagonists. These agents have proven to be safe and effective for use in preventing chemotherapy-induced nausea and vomiting [11]. Dolasetron mesylate (Anzemet, MDL 73,147EF; Marion Merrell Dow, Kansas City, Mo.) is a new highly selective addition to this drug class [9]. When administered intravenously, dolasetron is quickly cleared from the plasma with a median half-life of 9 min. The antiemetic effect of dolasetron appears to derive primarily from the metabolite MDL 74,156 (Fig. 1), which has a half-life of approximately

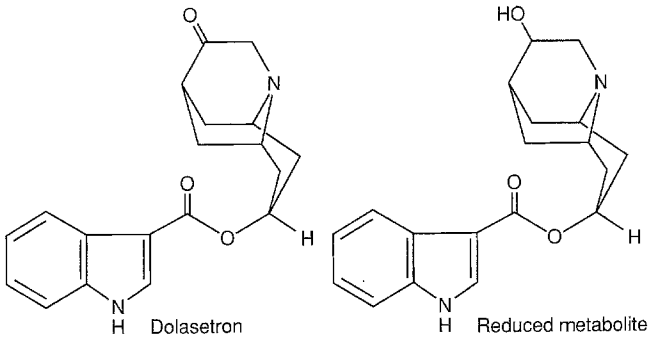

Fig. 1 Chemical structures of dolasetron (MDL 73,147) and its major metabolite (MDL 74, 156)

8 h and is more than 50 times as potent as the parent drug [3, 4]. In studies employing animal models, dolasetron has been shown to prevent cisplatin-induced emesis over a range of dose levels [8, 16]. Preliminary clinical trials have subsequently demonstrated significant antiemetic activity with dolasetron in cancer patients receiving cisplatin as the primary emetogenic challenge [6, 14]. Dolasetron has been well tolerated. Adverse effects have been mild and transient and similar in profile to those seen with other approved 5-HT_3 antagonists such as ondansetron and granisetron.

Very little information is available on the use of dolasetron in the setting of non-cisplatin chemotherapy. The present study was undertaken as a pilot evaluation of the efficacy and safety of dolasetron administered as a single intravenous (i.v.) dose over a dose range of 0.3–2.4 mg/kg in the prevention of acute nausea and vomiting in patients receiving cyclophosphamide and/or doxorubicin chemotherapy.

Patients and methods

Patients

Sixty-nine patients scheduled to receive appropriate chemotherapy were enrolled by the two participating institutions. Eligibility criteria included: histologically confirmed cancer; age ≥18 years; Karnofsky performance status ≥50%; normal serum potassium and calcium; chemotherapy to include cyclophosphamide (400–1200 mg/m^2) and/or doxorubicin (25–75 mg/m^2) infused over ≤60 min. Patients with any of the following were excluded from participation: history of significant neurologic or psychiatric illness except alcoholism; known seizure disorder; any emesis in the 24 h preceding chemotherapy; history of cardiomyopathy, congestive heart failure, or arrhythmias requiring antiarrhythmic medication; preexisting complete bundle branch block or heart block greater than first degree; history of emesis following any prior chemotherapy; pregnant women and women of childbearing age not using an accepted method of contraception; use of investigational drugs within 21 days of study entry or any drug with potential antiemetic action within 24 h of the start of study. Written informed consent was obtained from all participants, and the study was approved by the institutional review board of each institution.

Pretreatment evaluation included a complete medical history, physical examination, and electrocardiogram within 72 h of the start of chemotherapy. In addition, a clinical laboratory profile, including complete blood count, serum 12-channel biochemistry profile, and serum creatinine, was obtained within 1 week prior to the start of chemotherapy.

Drug dosing and administration

All patients in this study received cyclophosphamide (400–1200 mg/m^2) and/or doxorubicin (25–75 mg/m^2) infused i.v. over at least 60 min. Dolasetron was administered as a single IV dose of 0.3, 0.6, 1.2 or 1.8 mg/kg diluted to a total volume of 100 ml with 0.9% sodium chloride injection and infused over a 15- to 20-min period beginning 30 min prior to the start of chemotherapy. Dose levels were studied in ascending order with a planned enrollment of 15–20 patients per dose level. No formal early stopping rules for ineffective dose levels were planned. However, investigators reserved the right to prematurely terminate patient entry onto a given dose level if clearly sub-optimal antiemetic efficacy was noted. After completion of patient enrollment on the 1.8-mg/kg dose level, the study was amended to add an additional dose level of 2.4 mg/kg.

Patient evaluations

The antiemetic efficacy of dolasetron was assessed by monitoring the number and timing of vomiting and/or retching episodes over the 24-h period following the initiation of chemotherapy. An emetic episode was defined as one episode of vomiting or any number of retches within a 5-min period. For patients hospitalized during the study, these observations were performed by trained staff. Patients treated in an outpatient setting recorded these observations in a patient diary and received two follow-up phone calls during the study period by a trained study monitor to help with the assessment. Antiemetic efficacy was assessed as: complete (no emetic episodes and no rescue medication), major response (one or two emetic episodes and no rescue medication), or treatment failure (more than two emetic episodes and/or the use of rescue antiemetic medications).

Patients estimated the severity of nausea on a 100-mm visual analog scale (VAS), where 0 mm represents no nausea and 100 mm represents nausea as bad as it can be. This tool has been previously validated for antiemetic trials [5, 13]. Nausea was evaluated 15 min before dolasetron infusion, immediately prior to the start of chemotherapy, and 24 h after the start of chemotherapy. Patients were also asked to assess their satisfaction with antiemetic therapy at 24 h after the start of chemotherapy using a global evaluation scale developed for this study. This scale offered a choice of the following terms: very satisfied, satisfied, dissatisfied, or very dissatisfied.

Patients were monitored during the 24-h treatment period for possible adverse events. Laboratory studies performed pretreatment were repeated 24–48 h after the start of chemotherapy. In addition ECGs were repeated 1–2 h and 24–48 h after dolasetron administration.

Statistical analyses

All analyses utilized the intent-to-treat data set. The primary efficacy analysis was for a dose-related trend (one degree of freedom logistic regression test, controlling for investigator) in the proportion of complete responses to antiemetic therapy with dolasetron

Table 1 Patient characteristics

Characteristic	Dolasetron dose (mg/kg)					
	0.3 ($n=4$)	0.6 ($n=21$)	1.2 ($n=20$)	1.8 ($n=15$)	2.4 ($n=9$)	Total ($n=69$)
Age (years)						
Median	55.0	50.0	47.5	61.0	57.0	54.0
Range	27–64	25–70	25–76	30–81	40–75	25–81
Gender (%)						
Male	1 (25)	8 (38)	4 (20)	4 (27)	3 (33)	20 (29)
Female	3 (75)	13 (62)	16 (80)	11 (73)	6 (67)	49 (71)
Primary cancer site (%)						
Breast	2 (50)	12 (57)	14 (70)	6 (40)	4 (44)	38 (55)
Other	2 (50)	9 (43)	6 (30)	9 (60)	5 (56)	31 (45)
Primary chemotherapy (%)						
Doxorubicin	0	3 (14)	2 (10)	3 (20)	2 (22)	10 (15)
Cyclophosphamide	1 (25)	7 (33)	4 (20)	3 (20)	3 (33)	18 (26)
Both	3 (75)	11 (52)	14 (70)	9 (60)	4 (44)	41 (59)
Concomitant chemotherapy (%)						
5-FU	1 (25)	10 (48)	12 (60)	3 (20)	4 (44)	30 (43)
Vincristine	1 (25)	4 (19)	3 (15)	5 (33)	3 (33)	16 (23)
Methotrexate	0	6 (29)	2 (10)	1 (7)	1 (11)	10 (14)
Other	2 (50)	8 (38)	9 (45)	9 (60)	7 (78)	35 (51)

in patients monitored for at least 23.5 h following the start of chemotherapy. Subgroup analyses included the effects of age (<65 years vs ≥65 years), gender, and primary chemotherapy regimen on the proportion of complete responders as a function of dolasetron dose level. Secondary efficacy analyses were conducted using logistic regression controlling for investigator to analyze the proportion of complete or major responses. Changes from baseline in nausea (VAS) were evaluated by analysis of covariance, controlling for baseline and investigator. Patients' global evaluation results were examined for a trend in dose using a Mantel-Haenszel test for non-zero correlation. All tests of efficacy data were conducted using a nominal significance level of $\alpha=0.05$.

Safety data were evaluated by tests for linear trend across doses for the changes from baseline in ECG, vital signs and clinical laboratory test results using a two-way analysis of variance, controlling for investigator. All tests of safety data were conducted using a nominal significance level of $\alpha=0.10$.

Results

All 69 patients enrolled at the two study sites are included in the efficacy and safety analyses. Patient characteristics are listed in Table 1. Nearly three-quarters of the patients (71%) were female, and breast cancer (55%) was the most common primary neoplasm. Sixty-five patients (94%) were chemotherapy naive. Over one-half of the patients (59%) received both cyclophosphamide and doxorubicin. The most common additional concomitant chemotherapeutic agents were 5-fluorouracil (43%), vincristine (23%) and methotrexate (14%). The mean dose of methotrexate was 39.9 mg/m^2 (range 30–59 mg/m^2).

Antiemetic efficacy

The 0.3-mg/kg dose of dolasetron was found to be suboptimal after four patients had been treated at this level, and further patient entry was suspended. The original study design called for termination of the study after completion of patient enrollment at the 1.8-mg/kg dose level. The study was amended to include an additional (2.4-mg/kg) dose level. Further patient entry at this dose level was stopped after nine patients had been entered, to allow initiation of a larger randomized dose-ranging study.

Table 2 summarizes the results for each dose group with respect to antiemetic efficacy. Results from both study sites were similar. Sixty-five percent (45/69) of patients given dolasetron experienced either a complete or a major antiemetic response. No statistically significant differences among the five dose levels were found for the proportion of complete responders, and no significant trend in the proportion of complete responders relative to dolasetron dose was evident ($P=0.076$). Given the small number of patients entered onto the 0.3-mg/kg and 2.4-mg/kg dose arms, the power to detect a significant difference between the dose arms was low. Similarly, a test for trend in dose with respect to extent of nausea, as assessed by change from baseline for VAS at the end of the 24-h observation period, was not statistically significant. The global treatment evaluation, which ranked the patient's satisfaction with the treatment, showed that 46% of patients overall were 'very satisfied' and a further 28% were 'satisfied' with dolasetron as an antiemetic treatment.

Table 2 Antiemetic efficacy

Variable	Dolasetron dose (mg/kg)					
	0.3 ($n=4$)	0.6 ($n=21$)	1.2 ($n=20$)	1.8 ($n=15$)	2.4 ($n=9$)	Total ($n=69$)
Complete response (%)	1 (25)	14 (67)	9 (45)	12 (80)	6 (67)	42 (61)
Major response (%)	0 (0)	1 (5)	0 (0)	1 (7)	1 (11)	3 (4)
Complete or major response (%)	1 (25)	15 (71)	9 (45)	13 (87)	7 (78)	45 (65)
Median number of emetic episodes	>3	0	>3	0	0	0
Time to first emetic episode or rescue therapy (h)	9.1	>24.0	20.3	>24.0	>24.0	>24.0
Median nausea score[a]	38	0	37	0	0	2.0
Patients receiving rescue therapy (%)	3 (75)	6 (29)	10 (50)	2 (13)	2 (22)	23 (33)

[a] Change from baseline at 24 h, on a 100-mm visual analog scale (0=no nausea; 100=nausea as bad as it can be)

Table 3 Subgroup analyses for complete antiemetic response to dolasetron therapy. All *P* values are calculated from a logistic regression model with dose as a single-degree-of-freedom explanatory variable. *P* values shown are for the test for subgroup as main effect. There were no statistically significant interactions of subgroup variables and dose

Subgroup	Percentage of complete responders at each dolasetron dose (mg/kg)					
	0.3 ($n=4$)	0.6 ($n=21$)	1.2 ($n=20$)	1.8 ($n=15$)	2.4 ($n=9$)	Total ($n=69$)
Age						
<65 years ($n=57$)	25	63	39	78	71	56
≥65 years ($n=12$)	0	100	100	83	50	83
Age as main effect: $P=0.0082$						
Gender						
Male ($n=20$)	100	75	75	100	100	85
Female ($n=49$)	0	62	38	73	50	51
Gender as main effect: $P=0.0116$						
Primary chemotherapy						
Doxorubicin ($n=10$)	0	100	50	100	100	90
Cyclophosphamide ($n=18$)	100	86	75	100	100	89
Both ($n=41$)	0	45	36	67	25	41
Primary chemotherapy as main effect: $P=0.0017$						

Age, gender, and type of primary chemotherapy were significant predictors of complete control of emesis with dolasetron (Table 3). Patients under 65 years of age and females did significantly worse with respect to emesis control. In addition, patients receiving the combination of doxorubicin and cyclophosphamide did significantly worse than patients receiving either agent alone.

Safety

Table 4 lists the most common adverse events reported by patients during the study period. Dolasetron was well tolerated overall, and no dose-limiting toxicity was noted. All but one of the adverse events reported during the study were mild or moderate in intensity, and none was considered serious. Headache was the most common adverse event, reported by approximately one-half (49%) of patients. Other adverse events reported by three or more patients included lightheadedness and diarrhea, in four patients each, and chills, fever and dizziness, in three patients each.

Post-treatment ECG results were available 1–2 h and 24–48 h after dolasetron dosing for patients who received doses of 1.2 mg/kg and higher. As noted by others previously, treatment-related reductions in heart rate and minor increases in PR, QRS and QT_c intervals were observed [14]. All of these changes were asymptomatic, and none was considered clinically significant by the investigators. Examination of PR, QRS and QT_c interval results showed a significant effect of dolasetron dose only for the increase in PR interval at the 1- to 2-h post-dosing evaluation. Although the 1.2-mg/kg group had a median 1-ms decrease from baseline in the PR interval, the 1.8- and 2.4-mg/kg groups had median increases of 10 ms and 22 ms, respectively. For the QT_c interval, the median increases for the 1.2-, 1.8- and 2.4-mg/kg groups were 11, 27 and 39 ms, respectively.

Table 4 Adverse events reported as possibly/probably related to dolasetron therapy. Values represent the number (percentage) of subjects experiencing the adverse event. Subjects may have experienced more than one adverse event

Adverse event	Number (%) of patients reporting each adverse event for dolasetron dose (mg/kg)					
	0.3 ($n=4$)	0.6 ($n=21$)	1.2 ($n=20$)	1.8 ($n=15$)	2.4 ($n=9$)	Total ($n=69$)
Headache	3 (75)	12 (57)	6 (30)	11 (73)	2 (22)	34 (49.3)
Lightheadedness	1 (25)	1 (4.8)	2 (10)	0	0	4 (5.8)
Diarrhea	0	1 (4.8)	2 (10)	0	1 (11)	4 (5.8)
Dizziness	1 (25)	1 (4.8)	0	0	1 (11)	3 (4.3)
Chills	0	0	1 (5.0)	2 (13)	0	3 (4.3)
Fever	0	0	1 (5.0)	2 (13)	0	3 (4.3)
Fatigue	0	1 (4.8)	0	0	1 (11)	2 (2.9)
Nasal burning	0	2 (9.5)	0	0	0	2 (2.9)
Burning eyes	0	2 (9.5)	0	0	0	2 (2.9)

Mean alterations in vital signs were unremarkable and showed no statistically significant trend with respect to dolasetron dose.

Discussion

Previously reported studies have demonstrated significant antiemetic efficacy for dolasetron when used prior to cisplatin-based chemotherapy [6, 14]. In addition, dolasetron has exhibited a safety profile comparable to other selective 5-HT_3 antagonists such as ondansetron, granisetron and tropisetron [10]. Very little information is available on the potential utility and safety of dolasetron in the setting of non-cisplatin chemotherapy. In this trial, single IV doses of 0.6, 1.2, 1.8 and 2.4 mg/kg of dolasetron were effective in preventing emesis in patients receiving cyclophosphamide- and/or doxorubicin-based chemotherapy. Overall, 65% of patients treated at these dose levels remained completely free of emesis over the 24-h study period. The short median time to onset of emesis (9 h) and the severity of emesis noted in four patients entered on the 0.3-mg/kg dose level led to the early closure of this arm. At all other dose levels tested, the median time to first emetic episode was longer than 20 h, comparable to the results with other 5-HT_3 antagonists.

The primary objectives of this study were to assess safety and to explore, in a preliminary manner, a possible dose dependency of dolasetron for antiemetic efficacy. All doses studied in this trial had been previously shown to be well tolerated as a single IV dose in healthy volunteers [12]. No significant trend towards increased antiemetic efficacy or nausea control with increasing dolasetron dose was noted. A definitive dose comparison was not possible in this pilot trial, given the small number of patients treated at each dose level. Nevertheless, the proportion of patients protected from acute emesis compares favorably with similar clinical trials of ondansetron granisetron and tropisetron [2, 10]. For example, Beck et al. reported on the use of oral ondansetron in 237 patients receiving cyclophosphamide-based chemotherapy and noted a 63% rate of complete antiemetic protection [2].

Prior trials of dolasetron in patients receiving cisplatin demonstrated greater antiemetic efficacy with a dose of 1.8 mg/kg than with 0.6 mg/kg [14, 17]. Further escalation of dolasetron dose to 5.0 mg/kg resulted in increased adverse effects without further improvement in antiemetic efficacy [14]. Our inability to define a difference in efficacy between the 0.6-mg/kg and the 1.8-mg/kg dose may be a consequence of the small size of our trial. It may also reflect differences in the emetogenic challenge between these studies. A dose dependency for dolasetron may be more easily discernible with the greater emetogenic challenge provided with cisplatin-based chemotherapy. Definition of the optimal dose of dolasetron in the setting of non-cisplatin chemotherapy awaits the results of larger, randomized dose-finding studies, but our trial suggests that dose levels of 0.6–2.4 mg/kg are appropriate for further study.

In our trial, dolasetron was well tolerated at all five dose levels tested. As with other 5-HT_3 antagonists, headache was the most common adverse event. In all cases, the headaches were transient and not associated with any significant sequelae. Like the 5-HT_3 antagonists ondansetron and zatosetron, dolasetron has been associated with asymptomatic treatment-related ECG effects consistent with its electrophysiologic properties [18] (Marion Merrell Dow, Kansas City, Mo.; data on file). Prior clinical studies with dolasetron have demonstrated treatment-emergent ECG effects characterized by small increases in PR interval, QRS duration and QT_c interval at higher dose levels [1, 7, 14, 15]. These

changes were asymptomatic, transient and not considered clinically important. Preliminary data from recent studies indicate that ondansetron may produce similar asymptomatic ECG effects [1, 15].

Our study afforded the opportunity to assess the safety of dolasetron in patients receiving a chemotherapy agent (doxorubicin) with potential acute arrhythmogenic effects. Similar to prior trials, we noted slight prolongation of PR, QRS and QT_c intervals after dolasetron dosing. A statistically significant effect of dolasetron dose was observed only for increases in PR interval at 1–2 h after dosing. Although increases in QRS and QT_c intervals appeared to be dose-related, these changes were not statistically significant. The magnitude of change in ECG intervals was quite modest, with the mean change from baseline across both time periods and all dosage groups for PR, QRS and QT_c intervals less than 10.7%, 18.1% and 7.6%, respectively. All of the ECG changes noted were asymptomatic, transient, and not clinically significant. No episodes of tachyrhythmia, heart block (>grade 1), or heart failure occurred. Patients receiving doxorubicin did not experience any greater degree of ECG abnormalities than patients not treated with doxorubicin.

In conclusion, single IV doses of 0.6–2.4 mg/kg of dolasetron are safe and effective in the prevention of acute emesis in patients receiving cyclophosphamide and/or doxorubicin chemotherapy. In this study, dolasetron did not appear to potentiate the acute cardiotoxic effects of doxorubicin. Antiemetic efficacy is comparable to that reported for other 5-HT_3 antagonists in similar patient populations. Determination of a possible dose dependency of dolasetron for antiemetic efficacy awaits the completion of larger randomized dose-ranging studies.

Acknowledgements The authors acknowledge the editorial assistance of Marc Eisenberg, Ph.D., Gary McQuarrie, Pharm.D., Kathleen Smiley, Ph.D. and James Whitmore, Ph.D. This study was supported by a grant from Marion Merrell Dow Inc., Kansas City, Mo.

References

1. Baltzer L, Kris MG, Hinkley L, et al (1994) Reversible electrocardiographic interval prolongations following the specific serotonin antagonists ondansetron (OND) and dolasetron mesylate (DM): a possible drug class effect without sequelae? (abstract). Proc Am Soc Clin Oncol 13:433
2. Beck TM, Ciociola AA, Jones SE, et al (1993) Efficacy of oral ondansetron in the prevention of emesis in outpatients receiving cyclophosphamide-based chemotherapy. Ann Intern Med 118:407–413
3. Boeijinga PH, Galvan M, Baron BM, Dudley MW, Siegel BW, Slone AL (1992) Characterization of the novel 5-HT_3 antagonists MDL 73147EF (dolasetron mesylate) and MDL 74156 in NG108-15 neuroblastoma × glioma cells. Eur J Pharmacol 219:9–13
4. Boxenbaum H, Gillespie T, Heck K, Hahne W (1992) Human dolasetron pharmacokinetics. I. Disposition following single-dose intravenous administration to normal male subjects. Biopharm Drug Dispos 13:693–701
5. Clark R, Tyson L, Frisone M (1985) A correlation of objective (OBJ) and subjective (SUBJ) parameters in assessing antiemetic regimens (AER). Oncol Nurs Forum 12 [Suppl]:96
6. Conroy T, Cappelaere P, Fabbro M, et al (1994) Acute antiemetic efficacy and safety of dolasetron mesylate, a 5-HT_3 antagonist, in cancer patients treated with cisplatin. Am J Clin Oncol 17:97–102
7. Dixon R, Cramer M, Conway DW, et al (1995) Single-dose, placebo-controlled phase I study of oral dolasetron. Pharmacotherapy (in press)
8. Galvan M, Gittos MW, Miller RC, Moser PC, Giersbergen PLM van, Fozard JR (1992) Dolasetron mesilate (MDL 73147EF), a potent anti-emetic 5-HT_3 receptor antagonist (abstract). Br J Pharmacol 107 [Suppl]:449P
9. Gittos MW, Fatmi M (1989) Potent 5-HT_3 antagonists incorporating a novel bridged pseudopelletierine ring system. Actual Chim Ther 16:187–189
10. Grunberg SM, Hesketh PJ (1993) Control of chemotherapy-induced emesis. N Engl J Med 329:1790–1796
11. Hesketh PJ, Gandara DR (1991) Serotonin antagonists: a new class of antiemetic agents. J Natl Cancer Inst 83:613–620
12. Hunt TL, Cramer M, Shah A, Stewart W, Benedict CR, Hahne WF (1995) A double-blind, placebo-controlled, dose-ranging safety evaluation of single-dose intravenous dolasetron in healthy male volunteers. J Clin Pharmacol 35:705–712
13. Kris MG, Gralla RJ, Clark RA, Tyson LB, Groshen S (1987) Antiemetic control and prevention of side effects of anti-cancer therapy with lorazepam or diphenhydramine when used in combination with metoclopramide plus dexamethasone: a double-blind, randomized trial. Cancer 60:2816–2822
14. Kris MG, Grunberg SM, Gralla RJ, et al (1994) Dose-ranging evaluation of the serotonin antagonist dolasetron mesylate in patients receiving high-dose cisplatin. J Clin Oncol 12:1045–1049
15. Lifsey DS, Gralla RJ, Clark RA, Kline RC (1993) Electrocardiographic changes with serotonin antagonist antiemetics: rate of occurrence and clinical relevance (abstract). Proc Am Soc Clin Oncol 12:463
16. Miller RC, Galvan M, Gittos MW, Giersbergen PLM van, Moser PC, Fozard JR (1993) Pharmacological properties of dolasetron, a potent and selective antagonist at 5-HT_3 receptors. Drug Dev Res 28:87–93
17. Plezia P, Modiano M, Alberts D, et al (1992) A double-blind, randomized, parallel study of two doses of intravenous (IV) MDL 73,147EF in patients (PTS) receiving high dose cisplatin (CDDP)-containing chemotherapy (CT) (abstract). Proc Am Soc Clin Oncol 11:407
18. Williams PD, Cohen ML, Turk JA (1991) Electrocardiographic effects of zatosetron and ondansetron, two 5-HT_3 receptor antagonists, in anesthetized dogs. Drug Dev Res 24:277–284