Original article

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Efficacy, safety and pharmacokinetics of palonosetron in patients receiving highly emetogenic cisplatin-based chemotherapy: a dose-ranging clinical study

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Background: Although currently available 5-hydroxytryptamine type 3 receptor (5-HT_3) antagonists are effective, not all patients receiving these agents achieve adequate control of chemotherapy-induced nausea and vomiting (CINV). Palonosetron, a potent and highly selective 5-HT_3 antagonist with a strong affinity for 5-HT_3 and a prolonged plasma elimination half-life, may provide a longer duration of action than other approved agents.

Patients and methods: One hundred and sixty-one patients were randomly assigned to receive a single intravenous bolus dose of palonosetron (0.3, 1, 3, 10, 30 or 90 μg/kg) before administration of highly emetogenic chemotherapy, with no pretreatment with corticosteroids.

Results: The four highest doses of palonosetron were similarly effective during the first 24 h, producing clearly higher complete response (CR) (no emesis, no rescue medication) rates in the 3, 10, 30 and 90 μg/kg groups (46%, 40%, 50% and 46%, respectively) than in the 0.3–1 μg/kg group (24%) of evaluable patients (n = 148). The 3 μg/kg dose was identified as the lowest effective dose. A single dose of palonosetron showed prolonged efficacy in preventing delayed emesis, with approximately one-third of patients who received palonosetron 10 or 30 μg/kg maintaining a CR throughout the 7-day period following chemotherapy administration. Dose-proportional increases in pharmacokinetic parameters and a long plasma half-life (43.7–128 h) were observed. Palonosetron was well-tolerated, with no dose–response effect evident for the incidence or intensity of adverse events.

Conclusions: Palonosetron is an effective and well-tolerated agent for the prevention of CINV following highly emetogenic chemotherapy, with 3 and 10 μg/kg identified as the lowest effective palonosetron doses.

Key words: chemotherapy, dose-ranging, emesis, 5-hydroxytryptamine type 3 receptor antagonist, nausea, palonosetron

Introduction

Nausea and vomiting associated with highly emetogenic chemotherapy such as cisplatin-based regimens are mediated by 5-hydroxytryptamine release by gut enterochromaffin cells [1]. Emesis can be acute (occurring within 24 h of chemotherapy), delayed (beginning 24–48 h after chemotherapy), or in anticipation of chemotherapy [2]. Chemotherapy-induced nausea and vomiting (CINV) may result in dehydration, malnutrition or electrolyte imbalance, which can affect quality of life, the desire to continue antitumor therapy, and survival [3, 4]. Since their introduction, 5-hydroxytryptamine type 3 receptor (5-HT_3) antagonists have become the most frequently used agents in the control of emesis resulting from moderately to highly emetogenic chemotherapy [5]. Although 5-HT_3 antagonists are currently the standard therapy for preventing CINV, not all patients achieve adequate control with these agents, and those currently marketed agents have limited efficacy in the treatment of delayed emesis [2, 6, 7]. Therefore, there is a need to investigate new treatments and regimens in an effort to improve the therapeutic response.

Palonosetron is a potent and selective 5-HT_3 antagonist with a high affinity for 5-HT_3 receptors (pK_i = 10.45 in cultured mouse neuroblastoma–rat glioma hybridoma cells) [8] compared with granisetron (pK_i = 8.91 in cultured mouse neuroblastoma–rat glioma hybridoma cells) [8], ondansetron (pK_i = 8.39 in cultured mouse neuroblastoma–rat glioma hybridoma cells) [8], dolasetron (pK_i = 7.6 in cultured neuroblastoma glioma cells) [9], tropisetron (pK_i = 8.81 in cultured mouse neuroblastoma–rat glioma hybridoma cells) [8, 10], and azasetron (K_i = 0.33 nM in the small intestines of rats) [11]. In contrast to other 5-HT_3 antagonists that exist as racemic mixtures, palonosetron exists as a single stereoisomer, with improved pharmacological and pharmacokinetic profiles [12]. In preclinical studies, palonosetron demonstrated potent antiemetic properties in several standard animal models [13]. In

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previous phase I studies in healthy volunteers, intravenous (i.v.) palonosetron (0.3–90 μg/kg) was found to be well-tolerated, with mean plasma elimination half-life ($T_{1/2}$) values of ~40 h [13], substantially longer than that of ondansetron (4–6 h) [14], hydrodolasetron (the active metabolite of dolasetron; 7 h) [15], granisetron (5–8 h), tropisetron (7 h) and azasetron (9 h) [2, 16, 17]. Its high antiemetic potency, high binding affinity, and longer $T_{1/2}$ give palonosetron the potential to provide more complete and prolonged protection against CINV compared with currently available 5-HT_3 antagonists. The primary objective of this study was to determine the dose–response relationship of single i.v. doses of palonosetron (0.3–90 μg/kg) in chemotherapy-naive patients receiving highly emetogenic chemotherapy, in order to identify the lowest effective palonosetron dose that produces maximal efficacy. Additional objectives included the assessment of safety and the pharmacokinetics of palonosetron over the range of doses evaluated.

Subjects and methods

Subjects

Patients at least 18 years of age with histologically proven cancer who were chemotherapy-naive and scheduled to receive their first dose of highly emetogenic chemotherapy (≥70 mg/m^2 cisplatin or >1100 mg/m^2 cyclophosphamide) [18] were enrolled. Patients were required to have a Karnofsky performance status ≥60% and acceptable hepatic function (transaminases <2× upper limit of normal) and renal function (creatinine clearance ≥50 ml/min).

Exclusion criteria included severe, uncontrolled, concurrent illness other than neoplasia; unstable metastases to the brain; a history of seizures during adulthood; gastric outlet or intestinal obstruction; known vomiting within 24 h preceding palonosetron dosing; a known hypersensitivity to other 5-HT_3 antagonists; previous or current exposure to highly emetogenic chemotherapies (i.e. dacarbazine, nitrosoureas or mechlorethamine); and participation in another drug study or receipt of any investigational agents within 30 days of study entry. Patients were excluded if they had received, within 24 h before receipt of study medication, any antiemetic, sedative, corticosteroid, or other drug, that, in the opinion of the investigator, could influence the results of the study. All patients (men and women) were required to practice adequate contraception for 1 month after palonosetron dosing.

Study design

This was a randomized, double-blind, multicenter, parallel-design study conducted within the United States. Thirty minutes before the start of scheduled administration of highly emetogenic chemotherapy, patients received a single i.v. bolus of palonosetron 0.3, 1, 3, 10, 30 or 90 μg/kg over 30 s. Initial palonosetron dosing ranged from 0.3–30 μg/kg. However, because the lowest dose (0.3 μg/kg) was thought to possibly be too low to provide adequate protection against CINV, a protocol amendment eliminated the use of this dose and a 90 μg/kg dose group was added, without breaking the study-blind. Efficacy data from the two patients who received the 0.3 μg/kg dose were pooled with the 1 μg/kg group data. No concomitant corticosteroids were administered prophylactically. For ethical reasons, placebo was not a feasible option for a control group.

All patients were observed in the hospital or clinic for a minimum of 6 h after dosing and subsequently followed for 14 days after administration of palonosetron. Blood samples from patients at selected study sites were collected at specific intervals for pharmacokinetic analysis. The study protocol was approved by the Institutional Review Board of each participating study site. All patients provided written informed consent before being enrolled in the study.

Study visits and assessment procedures

During the week before palonosetron dosing, patients underwent a complete physical examination, laboratory assessment (i.e. hematology, blood chemistry, urinalysis), vital sign measurement, and 12-lead electrocardiogram (ECG). One hour before the start of chemotherapy, sitting blood pressure and heart rate were measured, and patients completed a pre-dose nausea assessment that consisted of a categorical scale of nausea (none, mild, moderate, or severe). Blood pressure and heart rate were measured 20 min before chemotherapy initiation, throughout the 6-h observation period following treatment, and at 24 h after the start of chemotherapy. Patients used diary cards to report the number of emetic episodes and degree of nausea at 2, 4, 8, 12 and 24 h after the start of chemotherapy, as well as time of their first emetic episode (if any). Patient satisfaction with control of nausea and vomiting was evaluated every 24 h via a 100-mm visual analog scale ranging from 0 (not at all satisfied) to 100 (completely satisfied). Patients were instructed to continue to record emetic episodes for 1 week after dosing and to rate, on a daily basis, the degree of nausea or the sensation of having to vomit and the degree of satisfaction with the control of nausea and vomiting.

Twenty-four hours following chemotherapy initiation, patients returned to the clinic (if not hospitalized) to report adverse events (AEs) and concomitant medications and to undergo a limited physical examination, a 12-lead ECG, blood tests and urinalysis. Patients again returned to the clinic 1 week after dosing for a limited physical examination, clinical laboratory evaluation, and a 12-lead ECG if the 24-h ECG was significantly different from the screening ECG. AEs and concomitant medications were recorded and diary cards were collected. All patients were contacted 14 days after dosing and questioned regarding nausea and vomiting, concomitant medications and AEs. Any AEs that persisted beyond the 14-day follow-up period were followed until resolution or explanation, or until 1 month after the dose.

Therapeutic response was evaluated by recording the occurrence of an emetic episode, the degree of nausea, and the need for rescue medication. An emetic episode was defined as (i) a single vomit of solid or liquid gastric contents; (ii) a single retch, or 'dry heave', that did not produce solid or liquid gastric contents; or (iii) any episode of continuous vomiting or retching. Episodes separated from each other by the absence of retching or vomiting for at least 1 min were considered separate emetic episodes. Rescue medication could be administered according to standard practice at each participating institution following the first emetic episode or succeeding episodes, or at the request of the patient. A complete response (CR) was defined as no emetic episode and no rescue medication; complete control (CC) was defined as no emetic episode, no rescue medication, and no more than mild nausea. Efficacy for acute (0–24 h) and delayed (2–7 days) CINV was determined. Treatment was considered to be a failure (i.e. unsatisfactory therapeutic response) if a patient had at least one emetic episode or received rescue medication.

For patients participating in the pharmacokinetic portion of the study, 7 ml of whole blood were drawn into heparinized vacuum tubes 30 min before, and 0.25, 0.5, 1, 2, 3, 4, 5, 6, 12, 24, 48, 72, 120 and 168 h after the administration of palonosetron. As only two patients received palonosetron 0.3 μg/kg, this dose level was not included in the pharmacokinetic portion of the study. Plasma was separated from whole blood by centrifugation and stored at –20°C. Plasma samples were assayed for palonosetron and its *N*-oxide metabolite (metabolite M9) using a validated high-pressure liquid chromatography method, with detection and quantification of each analyte via single-ion monitoring mass spectrometry. The lower limit of quantification was 0.020 ng/ml for palonosetron and 0.050 ng/ml for metabolite M9. Standard pharmacokinetic parameters were calculated by non-compartmental methods.

AEs occurring in the study were documented during the 24 h after dosing, on day 7, and on day 14. Events were assessed by the investigator for intensity

and possible association with study medication. All reported events were followed until the overall clinical outcome was ascertained or until 1 month after dosing.

The primary outcome variable was the proportion of patients with a CR during the 24-h period following the start of chemotherapy. This was also evaluated each day cumulatively for 7 days following chemotherapy. Secondary measures, assessed each day for 7 days after chemotherapy initiation, included: proportion of patients experiencing CC of emesis following the start of chemotherapy; time to treatment failure (first emetic episode or rescue medication); time to first emetic episode; time to rescue medication; number of patients free from emetic episodes and with a maximum of mild nausea; number of patients free of emetic episodes with no rescue medication; number of patients free from emetic episodes with no rescue medication and no nausea; and global assessment of nausea (assessed only at 24 h).

Study drug

Palonosetron was supplied in 5 ml glass vials at a concentration of 500 μg/ml, with normal saline provided for dilution. Before the dosing protocol amendment each dose was diluted with normal saline to 10 ml; subsequent to the amendment each dose was diluted to 25 ml. The label strength for all solutions was quantified as the free base.

Statistical analyses

The primary efficacy hypothesis of the study was that there was no difference in the proportion of patients with a CR between the 0.3 or 1 μg/kg dose and any of the higher i.v. doses (3, 10, 30 and 90 μg/kg). The number of patients to be included in the study was estimated to be 115 patients (23 patients for five dose groups), assuming a responder rate of the lowest dose group of 20% and a CR rate of the higher dose group of at least 70%.

Statistical analyses were carried out using SAS software, Version 6.08 (SAS Institute, Inc., Cary, NC, USA). Significance of group differences in efficacy parameters was determined at an alpha level of 0.05 using two-sided tests; comparability among groups with respect to baseline characteristics was made at the 0.10 level. The Cochran–Mantel–Haenszel test, stratified by center, was used to test the significance of differences in CR rates between the lowest-dose group (pooled 0.3 and 1 μg/kg doses) and each of the other dose groups. Additionally, a 95% confidence interval (CI) (adjusted for multiple CIs) for the true difference in CR rates between the combined 0.3 and 1 μg/kg groups and each of the other dose groups was obtained using Dunnett's method, modified for a dichotomous response [19]. Treatment group differences for the other binary efficacy variables were analyzed similarly. Comparisons in the time-to-event distributions were assessed using the log-rank test. The Wilcoxon rank-sum test was used for comparisons of the area under the categorical NIT curve, while tests involving overall assessment of nausea were based on the Cochran–Mantel–Haenszel test stratified by center. For the CR rate at 24 h, analyses were carried out for both intention-to-treat (ITT) and per-protocol (PP) populations; the other parameters were analyzed only for the evaluable patients (PP population). Safety data were tabulated and summarized descriptively. Maximum plasma concentration (C_{max}) and area under the plasma concentration–time curve (AUC) were tested for dose-proportionality with a one-way analysis of variance controlling for dose level. Dose proportionality of plasma elimination $T_{1/2}$, total body clearance (CL_T), and apparent volume of distribution (V_d) was evaluated without adjusting for dose.

Results

Patients

One hundred and sixty-one patients were enrolled in the study at 23 sites. All patients were included in the safety evaluation, while efficacy analyses were carried out on the ITT population (156 patients) and the PP population (148 patients). The majority (156 of 161) of enrolled patients received cisplatin (median dose 96 mg/m^2). To provide for a more homogeneous study population, the five patients who received cyclophosphamide-based therapy were excluded from efficacy analyses. An additional eight patients were excluded from efficacy analyses due to receipt of prohibited concomitant medication (four patients), low cisplatin dose and/or a slow infusion time (three patients), and patient unreliability (one patient).

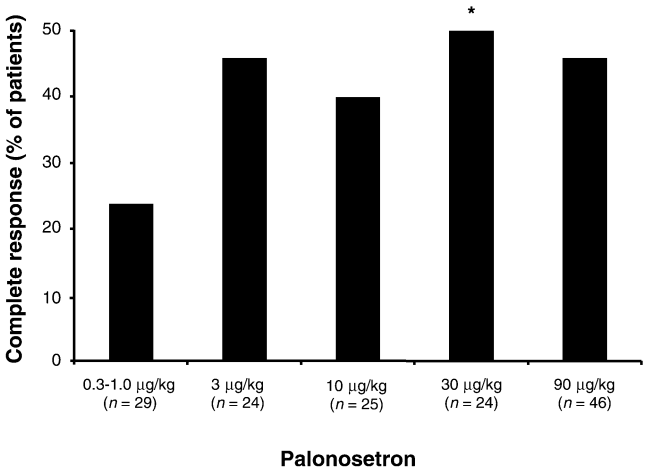

Figure 1. Complete response rates in the first 24 h following administration of a single intravenous dose of palonosetron (PP population). *$P \leq 0.05$ compared with palonosetron 0.3–1 μg/kg.

Patient characteristics are summarized in Table 1. Treatment groups were generally balanced with respect to demographic variables and medical history. There were no clinically meaningful differences between groups with regard to age, gender, race, weight, height, emetogenic chemotherapy agent, body surface area and tobacco and alcohol use within the past 6 months.

Efficacy

In the PP population, a CR was achieved in 24%, 46%, 40%, 50% and 46% of patients in the 0.3–1, 3, 10, 30 and 90 μg/kg groups, respectively, during the first 24 h following chemotherapy administration (Figure 1). The lowest-dose group (0.3–1 μg/kg) had a clearly inferior response rate compared with the higher-dose groups, with differences between groups reaching significance in the 30 μg/kg group ($P < 0.05$). Rates of CC were only slightly lower than rates of CR, with the lowest-dose group again appearing to show a lesser response to antiemetic therapy than those receiving the higher doses. The percentage of patients free from emetic episodes during the 24 h following chemotherapy ranged from 31% (for the 0.3–1 μg/kg group) to 58% (for the 3 and 30 μg/kg groups), with 29–57% of patients free from emetic episodes and experiencing none-to-mild nausea (0.3–1 μg/kg group and 30 μg/kg group, respectively). In general, about one-third of patients in the higher-dose groups experienced a total response (i.e. no emetic episodes, no rescue medication, and no nausea).

Table 1. Baseline demographic and clinical characteristics (enrolled patients)

Characteristic	Palonosetron dose (μg/kg)					Total (n = 161)
	0.3–1 (n = 32)	3 (n = 26)	10 (n = 26)	30 (n = 27)	90 (n = 50)	
Age (years)						
Mean ± SD	59 ± 10	60 ± 10	59 ± 13	61 ± 10	62 ± 11	60 ± 11
Range	37–75	43–75	30–77	40–79	23–78	23–79
Gender						
Male	26 (81%)	20 (77%)	21 (81%)	25 (93%)	37 (74%)	129 (80%)
Female	6 (19%)	6 (23%)	5 (19%)	2 (7%)	13 (26%)	32 (20%)
Race						
Caucasian	27 (84%)	21 (81%)	22 (85%)	20 (74%)	40 (80%)	130 (81%)
Black	3 (9%)	2 (8%)	3 (12%)	5 (19%)	8 (16%)	21 (13%)
Hispanic	1 (3%)	1 (4%)	1 (4%)	2 (7%)	2 (4%)	7 (4%)
Asian	0 (0%)	1 (4%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)
Other	1 (3%)	1 (4%)	0 (0%)	0 (0%)	0 (0%)	2 (1%)
Weight (kg)						
Mean ± SD	70 ± 17	73 ± 17	73 ± 13	74 ± 17	76 ± 20	74 ± 17
Range	45–121	48–105	49–113	47–104	39–132	39–132
Height (cm)						
Mean ± SD	175 ± 11	175 ± 8	174 ± 10	177 ± 8	172 ± 12	174 ± 11
Range	148–193	159–190	150–192	160–193	145–193	145–193
Body surface area (m^2)						
Mean ± SD	1.85 ± 0.25	1.88 ± 0.23	1.87 ± 0.19	1.90 ± 0.22	1.89 ± 0.27	1.88 ± 0.24
Range	1.46–2.4	1.49–2.29	1.5–2.41	1.56–2.3	1.3–2.5	1.3–2.5
Tobacco use (past 6 months)						
No	19 (59%)	13 (50%)	12 (46%)	16 (59%)	22 (44%)	82 (51%)
Yes	13 (41%)	13 (50%)	14 (54%)	11 (41%)	28 (56%)	79 (49%)
Alcohol use (past 6 months)						
None	17 (53%)	11 (42%)	9 (35%)	14 (52%)	25 (50%)	76 (47%)
Occasional	6 (19%)	7 (27%)	9 (35%)	7 (26%)	14 (28%)	43 (27%)
1–2 drinks/day	7 (22%)	4 (15%)	4 (15%)	3 (11%)	7 (14%)	25 (16%)
>2 drinks/day	2 (6%)	4 (15%)	4 (15%)	3 (11%)	4 (8%)	17 (11%)
Chemotherapy						
Cisplatin	31 (97%)	25 (96%)	26 (100%)	27 (100%)	47 (94%)	156 (97%)
Cyclophosphamide	1 (3%)	1 (4%)	0	0	3 (6%)	5 (3%)

SD, standard deviation.

Median time to first emetic episode was also longer in the four highest dose groups compared with the 0.3–1 μg/kg group. Median times to first emetic episode were statistically significantly higher in the 3, 30 and 90 μg/kg groups than in the lowest-dose group (P = 0.008, 0.012 and 0.007, respectively) (Table 2). Similarly, time to rescue medication was significantly longer in the 3, 30 and 90 μg/kg dose groups than in the 0.3–1 μg/kg group (P = 0.043, 0.022 and 0.015, respectively) (Table 2). When patients were assessed according to time to treatment failure (i.e. time to first emetic episode or time to rescue medication), the differences between the lowest-dose and the higher-dose groups were even more striking. Median time to treatment failure was 5.6, 22.7, 19.0, >24 and 21.8 h, respectively. Patients who received higher doses of palonosetron also experienced less nausea during the first 24 h after chemotherapy than those who received 0.3–1 μg/kg doses, with significant differences in the 3, 30 and 90 μg/kg groups.

A single dose of palonosetron showed prolonged efficacy in preventing delayed emesis, with approximately one-third of patients who received palonosetron 10 or 30 μg/kg maintaining a CR throughout the 7-day period following chemotherapy administration (Figure 2). These data suggest a prolonged efficacy of palono-

Table 2. Median time to first emetic episode, time to rescue medication and time to treatment failure (h) following administration of a single intravenous dose of palonosetron

	Palonosetron dose (μg/kg)				
	0.3–1 (n = 29)	3 (n = 24)	10 (n = 25)	30 (n = 24)	90 (n = 46)
Emetic episode	7.5	>24	19.5	>24	>24
P	–	0.008	0.186	0.012	0.007
Rescue medication	19	>24	>24	>24	>24
P	–	0.043	0.158	0.022	0.015
Treatment failure	5.6	22.7	19.0	>24	21.8
P	–	0.011	0.088	0.010	0.004

>24 h denotes a median that is undefined but >24 h, since <50% of patients had the event ≤24 h.

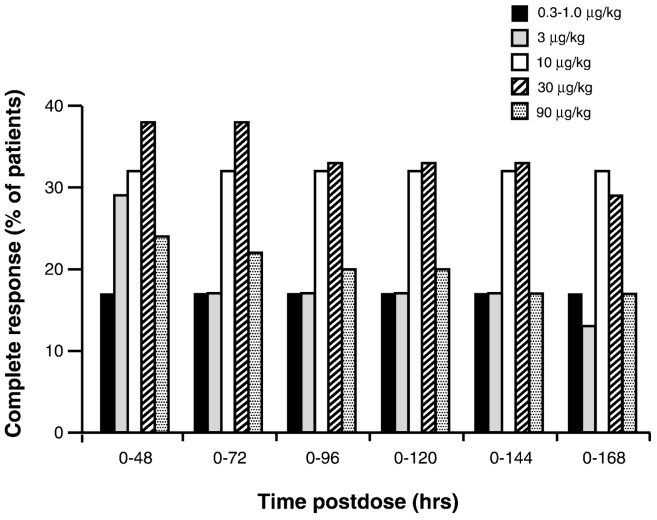

Figure 2. Effect of a single intravenous dose of palonosetron in preventing delayed emesis (complete response rates).

setron in the delayed phase of CINV. The proportion of patients who were free from emetic episodes throughout days 1–7 ranged from 26% to 38% for the four highest palonosetron doses, with 25–50% free from rescue medication.

Safety

One hundred and twenty-nine of 161 patients (80.1%) experienced at least one AE during the 14-day study period after administration of palonosetron, with the majority of AEs (86%) considered not related to the study medication. The most frequently reported drug-related AEs (i.e. adverse reactions) were headache and constipation (Table 3). Most AEs (83.9%) were rated as mild or moderate in intensity by the investigator. Serious AEs were reported for 25 patients (15.5%). However, none of these serious AEs were considered to be related to study drug; instead, they were usually considered to be secondary to the patient's chemotherapy or underlying disease. There was no apparent dose–response relationship for the occurrence of AEs. The incidence, intensity and relationship of AEs to study medication were generally similar between the various palonosetron dose levels, indicating no apparent dose–response relationship for the occurrence of AEs (data not shown). No clinically meaningful differences between treatment groups were observed for heart rate, blood pressure or other laboratory parameters evaluated. Results of ECG recordings showed no dose-dependent changes in any interval, including QT/QTc intervals (Table 4).

Pharmacokinetics

Available data allowed for calculation of palonosetron pharmacokinetics in 35 patients. Mean palonosetron plasma concentrations for the various dosage groups are illustrated in Figure 3 and the computed pharmacokinetic parameters of palonosetron and metabolite M9 are summarized in Table 5. Plasma palonosetron concentrations declined biexponentially—with an initial rapid distribution phase followed by a slower elimination from the body — and were measurable up to 168 h after the dose. Mean C_{max} values ranged from 0.89 to 336 ng/ml and were generally proportional to the dose. Similarly, AUC values increased dose-proportionally, with AUC from time zero to infinity ($AUC_{0-\infty}$) ranging from 13.8 ng•h/ml in the 1 μg/kg group to 957 ng•h/ml in the 90 μg/kg group. Mean CL_T of palonosetron ranged from 1.51 to 2.23 ml/min/kg, indicating low clearance compared with hepatic blood flow (approximately 20 ml/min/kg). V_d was large, with mean values ranging from 6.83 to 12.5 l/kg, consistent with extensive distribution into tissue. The low CL_T and large V_d resulted in a long $T_{1/2}$, with mean values ranging from 43.7 to 128 h. Although there was interpatient variability for many of the pharmacokinetic parameters, there were no statistically significant differences between dosage groups for any parameter, demonstrating dose-proportionality. Mean plasma concentrations of metabolite M9 were low relative to the parent compound, with plasma concentrations not measurable in most samples at the 1 and 3 μg/kg dose levels. Mean C_{max} values for metabolite M9 ranged from 0.055 to 0.855 ng/ml across the five dose levels. The ratios of $AUC_{0-\infty}$ for metabolite to parent drug averaged between 0.079 and 0.118.

Table 3. Most frequently reported treatment-related adverse events (≥2% overall incidence): values are no. of patients

	Palonosetron dose (μg/kg)					Total (n = 161)
	0.3–1 (n = 32)	3 (n = 26)	10 (n = 26)	30 g (n = 27)	90 (n = 50)	
Headache	9 (28.1%)	6 (23.1%)	4 (15.4%)	8 (29.6%)	4 (8.0%)	31 (19.3%)
Constipation	1 (3.1%)	3 (11.5%)	1 (3.8%)	3 (11.1%)	6 (12.0%)	14 (8.7%)
Abdominal pain	1 (3.1%)	0 (0%)	0 (0%)	1 (3.7%)	2 (4.0%)	4 (2.5%)
Dizziness	0 (0%)	0 (0%)	1 (3.8%)	2 (7.4%)	1 (2.0%)	4 (2.5%)

Table 4. Mean changes in electrocardiogram QT and QTc intervals (milliseconds) from baseline to 24 h after palonosetron dosing

	Palonosetron dose (μg)				
	1 (n = 22)	3 (n = 21)	10 (n = 19)	30 (n = 21)	90 (n = 35)
QT	–6	5	11	4	7
QTc (Fridericia correction)	–3	5	11	–1	6
QTc (Bazett correction)	–1	4	9	–4	4

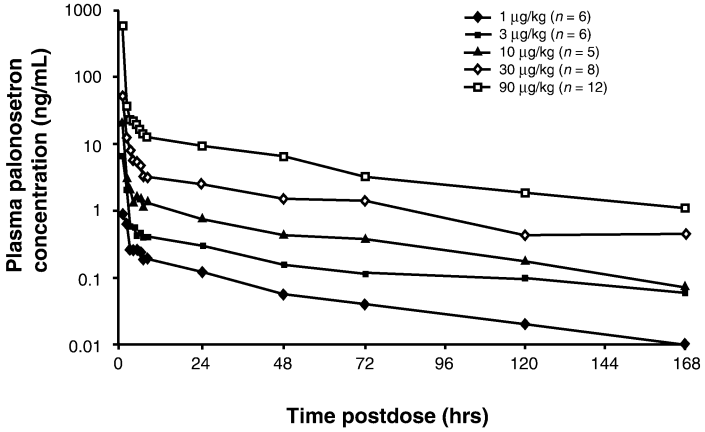

Figure 3. Mean plasma concentration of palonosetron after a single intravenous dose.

Discussion

The results of this study show that palonosetron, administered in the absence of pretreatment with corticosteroids, is an effective antiemetic agent among patients receiving highly emetogenic cisplatin-based chemotherapy. A CR (no emetic episode and no rescue medication) was achieved in 40–50% of the patients in the 3–90 μg/kg dose groups in the 24-h period following chemotherapy, with 39–48% of patients experiencing CC (no emetic episode, no rescue medication, and no more than mild nausea) during the same time period. A single i.v. dose of palonosetron also showed prolonged efficacy in preventing delayed emesis, with approximately one-third of patients who received palonosetron 10 or 30 μg/kg experiencing a CR through the 7 days after administration of chemotherapy. A dose–response relationship for efficacy of the higher doses of palonosetron was not observed at doses above the lowest effective dose of 3.0 μg/kg [20–25]. Similarly, with other 5-HT_3 antagonists, dose–response relationships for efficacy above a minimal threshold dose are generally not found. For example, a single i.v. dose of granisetron 40 μg/kg was found to be as effective as 160 μg/kg in three dose-ranging studies, with efficacy clearly lower at doses <10 μg/kg. Two studies of dolasetron also failed to demonstrate a dose–response relationship [24, 26], with one of the studies identifying a dose of 1.8 mg/kg as suboptimal [26]. Results of two dose-ranging studies of ondansetron are inconsistent, with one study reporting no difference in efficacy between a single i.v. dose of ondansetron 8 and 32 mg [25], and the other study reporting substantially greater efficacy with the higher dose following moderately and highly emetogenic chemotherapy [27].

Palonosetron was well-tolerated, with no unexpected AEs reported. Only a small proportion of events (approximately 15%) were considered possibly or probably related to study medication, with the majority (>80%) of AEs considered mild-to-moderate in intensity. Importantly, incidences, frequencies, intensities and drug relationships of AEs appear to be equally distributed among

Table 5. Pharmacokinetic parameters (means ± standard deviation) of palonosetron and metabolite M9 after administration of an intravenous dose in patients receiving chemotherapy

	Palonosetron dose (μg/kg)					*P*
	1 (*n* = 6)	3 (*n* = 6)	10 (*n* = 5)	30 (*n* = 8)	90 (*n* = 12)	
Palonosetron						
C_{max} (ng/ml)	0.89 ± 0.92	5.63 ± 5.48	13.0 ± 20.1	35.7 ± 37.0	336 ± 940	0.85
$T_{1/2}$ (h)	128 ± 93.8	56.4 ± 5.8	49.8 ± 14.4	86.4 ± 121	43.7 ± 12.2	0.20
$AUC_{0–24}$ (ng·h/ml)	4.17 ± 4.97	8.57 ± 4.22	26.6 ± 5.99	82.6 ± 25.5	310 ± 155	0.50
$AUC_{0–\infty}$ (ng·h/ml)	13.8 ± 7.58	35.8 ± 20.9	81.8 ± 23.9	348 ± 295	957 ± 450	0.42
CL_T (ml/min/kg)	1.51 ± 0.70	1.66 ± 0.59	2.23 ± 0.83	2.13 ± 1.21	1.90 ± 0.82	0.65
V_d (l/kg)	12.5 ± 4.19	7.91 ± 2.53	9.56 ± 4.21	9.18 ± 4.61	6.83 ± 2.67	0.08
Metabolite M9						
C_{max} (ng/ml)	0.055[a]	0.489[a]	0.141 ± 0.104	0.481 ± 0.262	0.855 ± 0.679	<0.001
$AUC_{0–\infty}$ (ng·h/ml)	NC	NC	NC	25.1 ± 11.3	72.7 ± 45.5	0.72
$AUC_{0–\infty}$ ratio (M9/palonosetron)	NC	NC	NC	0.118 ± 0.059	0.0789 ± 0.047	NC

[a]Data are means of parameters calculated from only two subjects.

$AUC_{0–24}$, area under the plasma concentration–time curve for hours 0–24; $AUC_{0–\infty}$, area under the plasma concentration-time curve for time 0 to infinity; CL_T, total body clearance; C_{max}, maximum plasma concentration; V_d, apparent volume of distribution; NC, not calculated.

the various palonosetron dose levels, with no apparent dose–response relationships.

Over the range of doses evaluated, both C_{max} and $AUC_{0–\infty}$ values increased with increasing dose in a dose-proportional manner, within the range 1–90 μg/kg. V_d of palonosetron was large (6.8–2.5 l/kg) and CL_T was low (1.51–2.23 ml/min/kg), resulting in a long plasma elimination $T_{1/2}$ (>44 h). The exposure of metabolite M9 relative to palonosetron as determined by AUC ratio was low (0.079–0.118). This finding, coupled with the negligible pharmacological activity of metabolite M9 (data on file), suggests that the antiemetic effect observed in patients is mainly due to palonosetron. Pharmacokinetics of palonosetron in this dose-ranging study were similar to studies in healthy volunteers [28], and are improved over other 5-HT_3 antagonists due to its long $T_{1/2}$, dose-proportional pharmacokinetics, large V_d, and low CL_T.

In summary, palonosetron showed substantial efficacy in the prevention of CINV in patients receiving highly emetogenic cisplatin-based chemotherapy. The prolonged protection observed with palonosetron in the management of chemotherapy-induced emesis following a single i.v. dose is particularly notable and is likely related to its strong binding affinity for 5-HT_3 receptors and its longer plasma elimination $T_{1/2}$. The pharmacokinetics of palonosetron in this study were similar to those previously reported in phase I trials. Based on the results of this dose-ranging study, fixed palonosetron doses of 0.25 mg (~3 μg/kg) and 0.75 mg (~10 μg/kg) are recommended for further evaluation, as they appear to be the lowest effective doses for the prevention of CINV in patients receiving highly emetogenic chemotherapy.

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