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A REVIEW ARTICLE ON PALONOSERTAN: ANTI-EMETIC DRUG

[1]R. Jona Methusala, [2]G. Rama subbaiah

Dr.K.V.Subbareddy Institute Of Pharmacy, Dupadu, Kurnool-518001.

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Abstract:

Palonosetron is a medication used to prevent nausea and vomiting, particularly associated with chemotherapy. It belongs to a class of drugs known as 5-HT3 receptor antagonists, which work by blocking the action of serotonin, a neurotransmitter involved in triggering nausea and vomiting. Palonosetron is known for its extended duration of action, making it effective for preventing delayed chemotherapy-induced nausea and vomiting. Palonosetron and its metabolites are mainly (to 80–93%) eliminated via the kidney. Biological half-life in healthy persons was 37±12 hours in a study, and 48±19 hours in cancer patients. In 10% of patients, half-life is over 100 hours. Most other marketed setrons have half-lives in the range of about two to 15 hours. Pharmacokinetics of palonosetron in this dose-ranging study were similar to studies in healthy volunteers [28], and are improved over other 5-HT3 antagonists due to its long T1/2, dose-proportional pharmacokinetics, large Vd, and low CLT. 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-HT3 receptors and its longer plasma elimination T1/2. 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.

Corresponding author:

Dr.R. Jona Methusala,

M. Pharm, Ph.D, Associate professor,
Department of Pharmacology,
Dr. K.V. Subba Reddy Institute Of Pharmacy,
Dupadu, Kurnool-518001.

QR CODE

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INTRODUCTON:

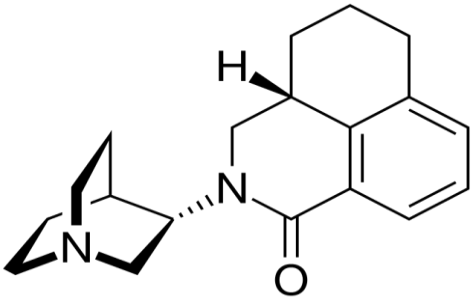
Palonosetron is a medication used to prevent nausea and vomiting, particularly associated with chemotherapy. It belongs to a class of drugs known as 5-HT3 receptor antagonists, which work by blocking the action of serotonin, a neurotransmitter involved in triggering nausea and vomiting. Palonosetron is known for its extended duration of action, making it effective for preventing delayed chemotherapy-induced nausea and vomiting.

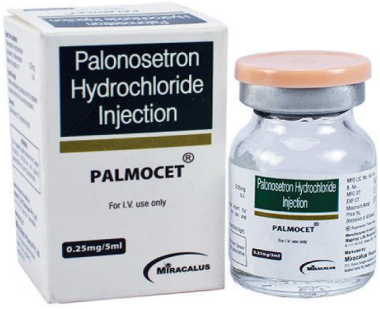
Discovery:

The interest in 5-HT3 receptor pharmacology surged when chemotherapies became first available (e.g.cisplatin approved in 1978 for ovarian and testicular cancers). At the time of their discovery in the 1980s, the first competitive antagonists were characterized as the "most potent drugs of any pharmacological class so far described, and less than a decade later the antiemetic research on 5-HT3 receptors was considered done by the pharma industry with numerous clinically and commercially successful drugs (coined -setrons). Beyond emesis, fundamental and pre-clinical research indicate that the 5-HT3 receptor plays a role in depression and in body weight control alosetron is used clinically to treat irritable bowel syndrome, Vortioxetene is an antidepressant non-selectively targeting the serotonin transporter and receptors. Fg-1

Characterization:

Chemical structure:





IUPAC NAME: (3aS)-2-[(3S)-1-azabicyclo [2.2. 2]octan-3-yl]-3a,4,5,6-tetrahydro-3H-benzo[de]isoquinolin-1-one; hydrochloride.

The substance is solid at room temperature and melts at 87 to 88 °C (189 to 190 °F). The infusions and capsules contain palonosetron hydrochloride which is also a solid. The hydrochloride is easily soluble in water, soluble in propylene glycol and slightly soluble in ethanol and isopropyl alcohol.

The molecule has two asymmetric carbon atoms. It is used in form of the pure (*S*,*S*)-stereoisomer

Pharmacokinetics:

Orally taken palonosetron is absorbed well from the gut and has a bioavailability of 97%. Highest blood plasma levels are reached after 5.1±1.7 hours, independently of food intake, and plasma protein binding is 62%. 40% of the substance are eliminated in the unchanged form, and a further 45–50% are metabolized by the liver enzyme CY Ap2d6 nd to a lesser extent by CYP3A4 and CYP3A. The two main metabolites, the *N*-oxide and a hydroxy derivative, have less than 1% of palonosetron's antagonistic effect and are thus practically inactive.

Palonosetron and its metabolites are mainly (to 80–93%) eliminated via the kidney. Biological half-life in healthy persons was 37±12 hours in a study, and 48±19 hours in cancer patients. In 10% of patients, half-life is over 100 hours. Most other marketed setrons have half-lives in the range of about two to 15 hours.

CPCSEA GUIDELINES FOR THE CARE AND USE OF LABORATORY ANIMALS:

GOAL:

The goal of these Guidelines is to promote the humane care of animals used in biomedical and behavioral research and testing with the basic objective of providing specifications that will enhance animal well-being, quality in the pursuit of advancement of biological knowledge that is relevant to humans and animals.

VETERINARY CARE:

Adequate veterinary care must be provided and is the responsibility of a veterinarian or a person who has training or experience in laboratory animal sciences and medicine. Daily observation of animals can be accomplished by someone other than a veterinarian; however, mechanism of direct and frequent communication should be adopted so that timely and accurate information on problems in animal health, behaviour, and well-being is conveyed to the attending veterinarian.

The veterinarian can also contribute to the

establishment of appropriate policies and procedures for ancillary aspects of veterinary care, such as reviewing protocols and proposals, animal husbandry and animal welfare; monitoring occupational health hazards containment, and zoonosis control programs and supervising animal nutrition and sanitation. Institutional requirements will determine the need for full-time or part-time or consultative veterinary services.

QUARANTINE, STABILIZATION AND SEPARATION

Quarantine is the separation of newly received animals from those already in the facility until the health and possibly the microbial status of the newly received animals have been determined. An effective quarantine minimizes the chance for introduction of pathogens into an established colony. A minimum duration of quarantine for small lab animals is one week and large animals is 6 weeks (cat, dog and monkey)Effective quarantine procedures should be used for non-human primates to help limit exposure of humans zoonotic infections.

Regardless of the duration of quarantine, newly received animals should be given a period for physiologic, psychological and nutritional stabilization before their use. The length of time stabilization will depend on the type and duration of animal transportation, the species involved and the intended use of the animals. Physical separation of animals by species is recommended to prevent interspecies disease physiological and behavioral changes due to interspecies conflict. Such separation is usually accomplished by housing different species in separate rooms; however, cubicles, laminar-flow units, cages that have filtered air or separate ventilation, and isolators shall be suitable alternatives. In some instances, it shall be acceptable to house different species in the same room, for example, if two species have a similar pathogen status and are behaviourally compatible.

SURVEILLANCE, DIAGNOSIS, TREATMENT AND CONTROL OF DISEASE

All animals should be observed for signs of illness, injury, or abnormal behaviour by animal house staff. As a rule, this should occur daily, but more-frequent observations might be warranted, such as during postoperative recovery or when animals are ill or have a physical deficit. It is imperative that appropriate methods be in place for disease surveillance and diagnosis (Annexure 1 and 2).

Unexpected deaths and signs of illness, distress, or other deviations from normal health condition in animals should be reported promptly to ensure appropriate and timely delivery of veterinary medical care. Animals that show signs of a contagious disease should be isolated from healthy animals in the colony. If an entire room of animals is known or believed to be exposed to an infectious agent (e.g. Mycobacterium Tuberculosis in non-human primates), the group should be kept intact and isolated during the process of diagnosis, treatment, and control. Diagnostic clinical laboratory may be made available.

ANIMAL EXPERIMENTATION INVOLVING HAZARDOUS AGENTS

Institutions should have policies governing experimentation with hazardous agents. Institutional Bio safety Committee whose members are knowledgeable about hazardous agents are in place in most of the higher level education, research institutes and in many pharmaceutical industries for safety issues. This committee shall also examine the proposal on animal experiments involving hazardous agents in addition to its existing functions (Annexure– 8).Since the use of animals in such studies requires special consideration, the procedures and the facilities to be used must be reviewed by both the Institutional Bio safety Committee and Institutional Animal Ethics Committee (IAEC).

DURATIONS OF EXPERIMENTS

No animal should be used for experimentation for more than 3 years unless adequate justification is provided.

PHYSICAL RESTRAINT

Brief physical restraint of animals for examination, collection of samples, and a variety of other clinical and experimental manipulations can be accomplished manually or with devices be suitable in size and design for the animal being held and operated properly to minimize stress and avoid injury to the animal. Prolonged restraint of any animal, including the chairing of non-human primates, should be avoided unless essential to research objectives. Less restrictive systems, such as the tether system or the pole and collar system, should be used when compatible with research objectives.

The following are important guidelines for the use of restraint equipments: Restraint devices cannot be used simply as a convenience in handling or managing animals.

The period of restraint should be the minimum

required to accomplish the research objectives. Animals to be placed in restraint devices should be given training to adapt to the equipment. Provision should be made for observation of the animal at appropriate intervals. Veterinary care should be provided if lesions or illness associated with restraint are observed. The presence of lesions, illness, or severe behavioral change should be dealt with by the temporary or permanent removal of the animal from restraint.

PHYSICAL FACILITIES:

(a) **Building materials**: should be selected to facilitate efficient and hygienic operation of animal facilities. Durable, moisture-proof, fire-resistant, seamless materials are most desirable for interior surfaces including vermin and pest resistance.

(b) Corridor(s): should be wide enough to facilitate the movement of personnel as well as equipments and should be kept clean.

(c) Utilities: such as water lines, drain pipes and electrical connections should preferably be accessible through service panels or shafts in corridors outside the animal rooms. (d) Animal room: doors should be rust, vermin and dust proof. They should fit properly within their frames and provided with an observation window. Door closures may also be provided. Rodent barriers can be provided in the doors of the small animal facilities.

(e) Exterior windows: Windows are not recommended for small animal facilities. However, where power failures are frequent and backup power is not available, they may be necessary to provide alternate sources of light and ventilation. In primate rooms, windows can be provided.

(f) Floors: Floors should be smooth, moisture proof, nonabsorbent, skid-proof, resistant to wear, acid, solvents, adverse effects of detergents and disinfectants. They should be capable of supporting racks, equipment, and stored items without becoming gouged, cracked, or pitted, with minimum number of joints. A continuous moisture-proof membrane might be needed. If sills are installed at the entrance to a room, they should be designed to allow for convenient passage of equipment.

(g) Drains: Floor drains are not essential in all rooms used exclusively for housing rodents. Floor in such rooms can be maintained satisfactorily by wet vacuuming or mopping with appropriate disinfectants or cleaning compounds. Where floor drains are used, the floors should be sloped and drain taps kept filled with water or corrosion free mesh. To prevent high humidity, drainage must be adequate to allow rapid removal of water and drying of surfaces.

(h) Walls and ceilings: Walls should be free of cracks, unsealed utility penetrations, or imperfect junctions with doors, ceilings, floors and corners. Surface materials should be capable of withstanding scrubbing with detergents and disinfectants and the impact of water under high pressure.

Pre clinical studies:

In preclinical studies, palonosetron demonstrated potent antiemetic properties in several standard animal models . In 331 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 (T1/2) values of ∼40 h , substantially longer than that of ondansetron (4–6 h), hydrodolasetron (the active metabolite of dolasetron; 7 h), granisetron (5–8 h), tropisetron (7 h) and azasetron (9 h) . Its high antiemetic potency, high binding affinity, and longer T1/2 give palonosetron the potential to provide more complete and prolonged protection against CINV compared with currently available 5-HT3 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 histological proven cancer who were chemotherapy-naive and scheduled to receive their first dose of highly emetogenic chemotherapy (≥70 mg/m2 cisplatin or >1100 mg/m2 cyclophosphamide) [18] were enrolled. Patients were required to have a Karnofsky performance status ≥60% and acceptable hepatic function (transaminases]. 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-HT3 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 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 mg/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 332 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 meddication; 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.

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 (Cmax) 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 T1/2, total body clearance (CLT), and apparent volume of distribution (Vd) was evaluated without adjusting for dose.

RESULTS:

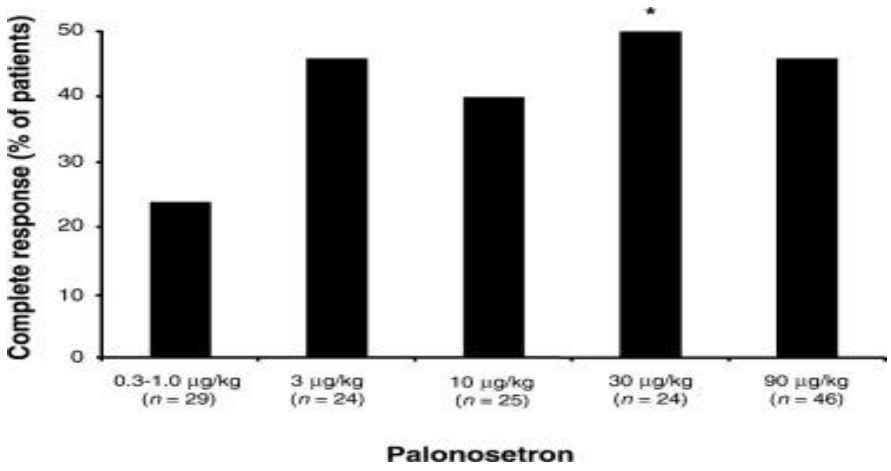
Patients:

One hundred and sixty-one patients were enrolled in the study at 23 sites. All patients were included in the safety evaluation, whileefficacy 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/m2). 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). 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.

fig-2



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.

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%)

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)	
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%)

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).

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 lowestdose 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 palonosetron 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.

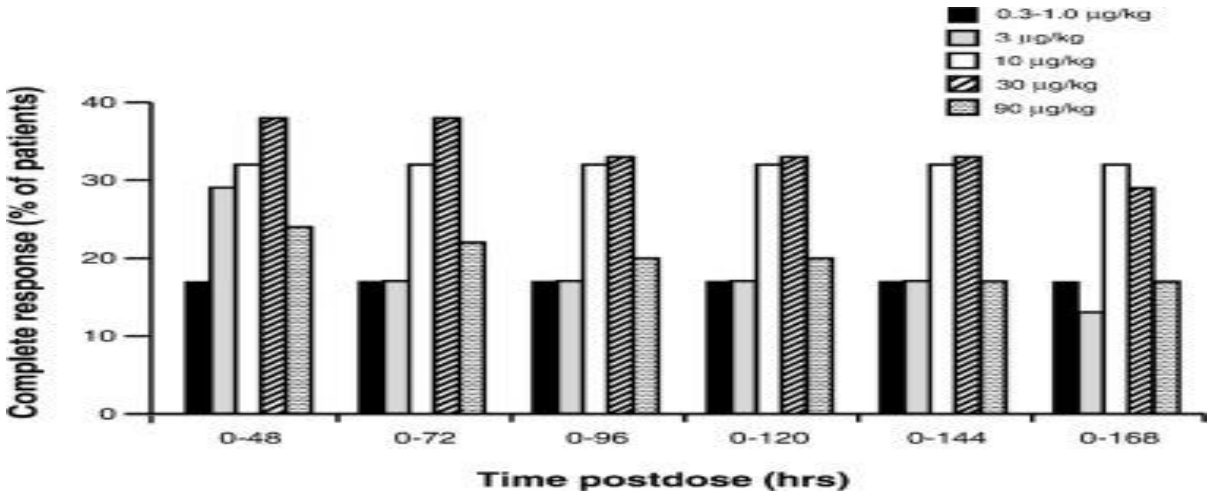
TABLE 2

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.

fig-3

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.

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 Cmax 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 (AUC0–∞) 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 CLT 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).

Vd was large, with mean values ranging from 6.83 to 12.5 l/kg, consistent with extensive distribution into tissue. The low CLT and large Vd resulted in a long T1/2, 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 Cmax values for metabolite M9 ranged from 0.055 to 0.855 ng/ml across the five dose levels. The ratios of AUC0 for metabolite to parent drug averaged b etween 0.079 and 0.118.

Table-3

Palonosetron dose (µg/kg)					Empty Cell	**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%)

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-HT3 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 80%) of AEs considered mild-to-moderate in intensity. Table-4:

Importantly, incidences, frequencies, intensities and drug relationships of AEs appear to be equally distributed amongthe various palonosetron dose levels, with no apparent dose– response relationships.

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

	Palonosetron dose (µg/kg)					Empty Cell	***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

Over the range of doses evaluated, both Cmax and AUC0–∞ values increased with increasing dose in a dose-proportional manner, within the range 1–90 µg/kg. Vd of palonosetron was large (6.8–2.5 l/kg) and CLT was low (1.51–2.23 ml/min/kg), resulting in a long plasma elimination T1/2 (>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-HT3

antagonists due to its long T1/2, dose-proportional pharmacokinetics, large Vd, and low CLT. 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-HT3 receptors and its longer plasma elimination T1/2. 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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