Clinical evaluation of two antiemetic combinations palonosetron dexamethasone versus ondansetron dexamethasone in chemotherapy of head and neck cancer

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ABSTRACT

Introduction: Palonosetron and ondansetron are two selective 5-hydroxytryptamine (5-HT3) receptor antagonists that have shown remarkable efficacy in controlling nausea and vomiting following administration of moderately emetic anticancer chemotherapy. Their efficacy is enhanced by the concurrent administration of dexamethasone. In the present study, we aimed to compare the antiemetic efficacy of a palonosetron plus dexamethasone (PD) schedule versus an ondansetron plus dexamethasone (OD) schedule.

Methods: A randomised, crossover trial was conducted in 30 patients with head and neck cancer who were receiving moderately emetogenic chemotherapy. The patients were divided into two groups. In the first cycle, one group was given a PD schedule and the other, an OD schedule. For the subsequent cycle, crossover of the antiemetic schedules was done. The antiemetic effects were evaluated by recording the intensity of nausea and the frequency of vomiting in the acute and delayed phases.

Results: Complete response in the acute phase was observed in 83.3 percent of the patients on the PD schedule and in 80 percent of those on the OD schedule. In the delayed phase, complete response was observed in 76.7 percent and 66.7 percent of the patients on the PD schedule and OD schedule, respectively. The overall rate of complete response was 66.7 percent in the PD group and 46.7 percent in the OD group. In the PD group, there were 73.3 percent of nausea-free patients as opposed to 66.7 percent in the OD group.

Conclusion: The results suggest that the PD schedule was superior to the OD schedule in controlling emesis in cancer chemotherapy, although this difference was not statistically significant.

Keywords: acute emesis, delayed emesis, dexamethasone, ondansetron, palonosetron

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INTRODUCTION

Nausea and vomiting (emesis) are overwhelming side effects of treatment with antineoplastic agents. Chemotherapy-induced nausea and vomiting are so distressing to some patients after repeated cycles of treatment that they become habituated to develop these symptoms even before the treatment is given.[1] Moreover, nausea and vomiting can cause metabolic imbalances, a decline in functional ability, nutrient depletion, anorexia, a decrease in the patient's performance and mental status, as well as complications like wound dehiscence and esophageal tear.[1]

Selective 5-hydroxytryptamine (5-HT3) receptor antagonists are very effective for the prevention and treatment of nausea and vomiting associated with cancer chemotherapy and radiotherapy in cancer patients, as the release of neurotransmitter serotonin (5-HT) is believed to be the main culprit of emesis. Chemotherapeutic agents release serotonin from enterochromaffin cells, which activate the serotonergic receptors on visceral afferent fibres to induce emesis. 5-HT3 receptor antagonists block the activation of 5-HT3 receptors in the gut as well as in the area postrema (CTZ) and vomiting centre, thus possessing both peripheral and central action. They have significantly improved the control rates for acute nausea and vomiting associated with emetogenic chemotherapy.[2] 5-HT3 receptor antagonists alone have been shown to

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Table I. Dosing schedule of the enrolled patients (n = 30).

Schedule	Dose
PD	Palonosetron 0.25 mg iv plus dexamethasone 16 mg iv (half an hour before chemotherapy)
OD	Ondansetron 16 mg iv plus dexamethasone 16 mg iv (half an hour before chemotherapy)

prevent acute vomiting in 40%–60% of patients receiving higher doses of cisplatin (> 50 mg/m^2), and the co-administration of dexamethasone significantly prevents acute vomiting in 60%–90% of patients.[3] Although a number of mechanisms have been proposed, the exact mechanism of the antiemetic action of corticosteroids when administered singly or in combination is not clear.[4]

First-generation 5-HT3 receptor antagonists, ondansetron, granisetron, dolasetron and tropisetron have comparable efficacies in preventing acute chemotherapy-induced nausea and vomiting, but they have limited impact on delayed symptoms.[5] The second-generation 5-HT3 receptor antagonist, palonosetron, is a potent and selective antagonist with a high affinity for 5-HT3 receptors.[6] In addition to being more efficacious against chemotherapy-induced acute nausea and vomiting, it also shows improved efficacy in preventing these delayed symptoms.[7] It has been postulated that the superior clinical efficacy of palonosetron may be due to its 30 times higher binding affinity for the 5-HT3 receptor subtype and its 4–10 times longer half life, compared to the first-generation 5-HT3 receptor antagonists. The superior effect of palonosetron on delayed complete response may be due to its greater acute antiemetic efficacy, as it has been hypothesised that a significant predictive factor for delayed chemotherapy-induced nausea and vomiting is the presence of acute chemotherapy-induced nausea and vomiting.[8,9] Presently, palonosetron is the only drug of this group that has a specific indication for the prevention of chemotherapy-induced delayed nausea and vomiting in patients receiving moderately emetogenic drugs.[10] Hence, the present study was undertaken to compare the antiemetic effect of palonosetron with ondansetron in cancer chemotherapy-induced emesis.

METHODS

This was an open, randomised, crossover trial conducted in 30 adult patients aged 25–60 years who were receiving moderately emetogenic cancer chemotherapeutic drugs at the Department of Radiotherapy, Post Graduate Institute of Medical Sciences, Rohtak, India. All these patients had histologically confirmed head and neck cancers. Informed consent was obtained from all the patients before the start of the study, and they were free to withdraw at any time without prejudice to further treatment.

The following patients were not included in the study: (1) Patients on antiemetic therapy who developed nausea and vomiting 24 hours prior to cancer chemotherapeutic drug administration, or had nausea and vomiting due to any other causes, e.g. intestinal obstruction, uraemia, raised intracranial pressure; (2) Patients who had several concurrent illnesses other than neoplasms, e.g. acute peptic ulcer, severe diabetes mellitus; (3) Patients who were on concurrent therapy with corticosteroids; (4) Patients with grossly abnormal liver function tests except when attributed to liver metastasis; and (5) Pregnant patients.

All the patients received the same standard chemotherapy regimen, consisting of intravenous docetaxel 60 mg/m^2 (Docetax, Cipla Pharmaceuticals, Mumbai, India), intravenous carboplatin 300 mg/m^2 (Cytocarb, Cipla Pharmaceuticals, Mumbai, India) and intravenous 5-fluorouracil 600 mg/m^2 (Fluracil, Biochem Pharmaceuticals, Mumbai, India). For prophylaxis and control of cancer chemotherapy-induced emesis, the patients were administered antiemetic schedules (Table I). Half of the patients received a PD schedule consisting of palonosetron (Palostar, Lupin Pharmaceuticals, Mumbai, India) plus dexamethasone (Deksa, Intas Pharmaceuticals, Ahmedabad, India) and the remaining half received an OD schedule consisting of ondansetron (Emeset, Cipla Pharmaceuticals, Mumbai, India) plus dexamethasone. The simple standard technique for random assignment using a table of random numbers was used to allocate the treatment schedule. For the subsequent cycle, a crossover of the antiemetic schedules was done.

The evaluation of the effectiveness of antiemetic therapy was done by careful recording of the frequency of acute emesis (vomiting within 24 hours of chemotherapy), delayed emesis (vomiting commencing from 24 hours up to five days or more) and overall response from Day 1–5. Similarly, the intensity of nausea was carefully assessed during the acute (nausea within 24 hours of chemotherapy), delayed (nausea commencing from 24 hours up to five days) and overall (nausea from Day 1–5) phases. Patients who did not report any nausea were recorded as nausea-free patients. The number of nausea-free patients was recorded on Day 1–5.

The recording of acute nausea and vomiting was carried out at the hospital, while the frequency and intensity of delayed nausea and vomiting were recorded by the patients' relatives, who were provided with detailed

Table II. Distribution of patients in different grades of antiemetic responses in two combination therapies (n = 30).

	No (%)		
	Acute phase (Day 1)	Delayed phase (Day 2–5)*	Overall response (Day 1–5)
PD Schedule			
Complete Response[a]	25 (83.3)	23 (76.7)	20 (66.7)
Major Response[b]	1 (3.3)	1 (3.3)	2 (6.7)
Minor Response[c]	2 (6.7)	2 (6.7)	2 (6.7)
Failure[d]	2 (6.7)	4 (13.3)	6 (20.0)
OD Schedule			
Complete Response[a]	24 (80.0)	20 (66.7)	14 (46.7)
Major Response[b]	2 (6.7)	2 (6.7)	4 (13.3)
Minor Response[c]	2 (6.7)	3 (10.0)	5 (16.7)
Failure[d]	2 (6.7)	5 (16.7)	7 (23.3)

* Delayed response is taken depending upon the worst response from Day 2–5.
[a] no vomiting; [b] 1–2 times; [c] 3–5 times; [d] > 5 times of vomiting
PD: palonosetron plus dexamethasone; OD: ondansetron plus dexamethasone

Table III. Distribution of patients in different grades of nausea control responses in the two combination therapies (n = 30).

	No (%)		
	Acute phase (Day 1)	Delayed phase (Day 2–5)*	Overall response (Day 1–5)
PD Schedule			
No nausea (0)	22 (73.3)	19 (63.3)	16 (53.3)
Mild nausea (+)	2 (6.7)	4 (13.3)	4 (13.3)
Moderate nausea (++)	3 (10.0)	5 (16.7)	5 (16.7)
Severe nausea (+++)	3 (10.0)	2 (6.7)	5 (16.7)
OD Schedule			
No nausea (0)	20 (66.7)	17 (56.7)	11 (36.7)
Mild nausea (+)	3 (10.0)	4 (13.3)	5 (16.7)
Moderate nausea (++)	3 (10.0)	5 (16.7)	6 (20.0)
Severe nausea (+++)	4 (13.3)	4 (13.3)	8 (26.7)

* Delayed response is taken depending upon the worst response from Day 2–5.
PD: palonosetron plus dexamethasone; OD: ondansetron plus dexamethasone

explanation of the procedure. They were instructed to record the frequency of emesis on the protocols provided, which were then collected at the next hospital visit. To evaluate the intensity, the patients were instructed to place a finger at a point on the descriptive ordinal scale (DS), depending on the intensity of nausea felt by them.

The assessment of response was conducted according to the criteria of Jones et al.[11] The control of vomiting was graded as complete response: no emetic episode; major response: one or two emetic episodes; minor response: 3–5 emetic episodes; and failure: > 5 emetic episodes. The intensity of nausea was evaluated on a four-point DS,[12] with no nausea at one end and severe nausea (+++) at the other end. The criteria adopted for control of nausea were: no nausea (0); mild nausea (+); moderate nausea (++); and severe nausea (+++). The patients were categorised according to the intensity of nausea and frequency of vomiting experienced, and the results were analysed by applying the chi-square test.

RESULTS

The different grades of antiemetic responses obtained in the PD and OD schedules are described below. Complete response in the acute phase was observed in 25/30 (83.3%) patients on the PD schedule and in 24/30 (80.0%) patients on the OD schedule. In the delayed phase, complete response was observed in 23/30 (76.7%) patients in the PD schedule vs. 20/30 (66.7%) in the OD schedule. The overall rate of complete response for emesis was slightly better in the PD schedule group, at 66.7% (20/30) as compared to 46.7% (14/30) in the OD schedule group. The failure rate in the acute phase was similar in the PD

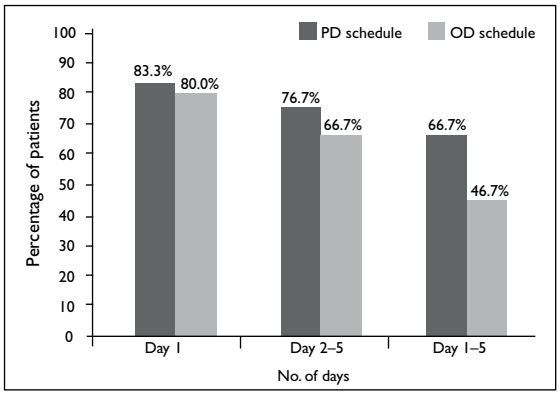

Fig. 1 Graph shows the percentage of complete response rate of emesis following treatment with palonosetron plus dexamethasone (PD) vs. ondansetron plus dexamethasone (OD).

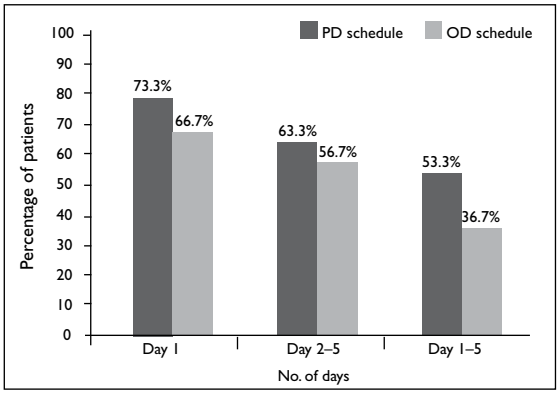

Fig. 2 Graph shows the percentage of nausea-free patients in the acute, delayed and overall phases following treatment with palonosetron plus dexamethasone (PD) vs. ondansetron plus dexamethasone (OD).

and OD schedule groups, i.e. at 6.7% (2/30).

In the delayed phase, 4/30 (13.3%) patients receiving the PD schedule experienced failure of emesis control vs. 5/30 (16.7%) patients who were receiving the OD schedule. Overall, the failure rate of emesis control was slightly lower in the PD schedule group, at 20.0% (6/30) compared to 23.3% (7/30) in the OD schedule group, as shown in Table II and Fig. 1. Thus, the overall control of vomiting in the PD schedule group was better than that in the OD schedule group, but this difference was not found to be statistically significant.

In terms of nausea control, complete response in the acute phase was observed in 22/30 (73.3%) patients on the PD schedule and in 20/30 (66.7%) patients on the OD schedule. In the delayed phase, complete response was observed in 19/30 (63.3%) patients on the PD schedule vs. 17/30 (56.7%) on the OD schedule. The overall complete response in the PD schedule group was much better, at 16/30 (53.3%) as opposed to 11/30 (36.7%) in the OD schedule group.

Failure rate in the acute phase was 3/30 (10.0%) in the PD schedule group and 4/30 (13.3%) in the OD schedule group, while in the delayed phase, the failure rate was 2/30 (6.7%) and 4/30 (13.3%) in the PD and OD schedule groups, respectively. Overall, the failure rate of nausea control was lower in the PD schedule group, at 16.7% (5/30), as opposed to 26.7% (8/30) in the OD schedule group. The number of nausea-free patients was greater in the PD schedule group as compared to the OD schedule group in the acute (73.3% vs. 66.7%), delayed (63.3% vs. 56.7%) and overall (53.3% vs. 36.7%) phases, as shown in Table III and Fig. 2. The distribution of nausea-free patients according to days is shown in Fig. 3. Thus, the overall control of nausea was better in the PD schedule group than in the OD schedule group, but this difference was not found to be statistically significant.

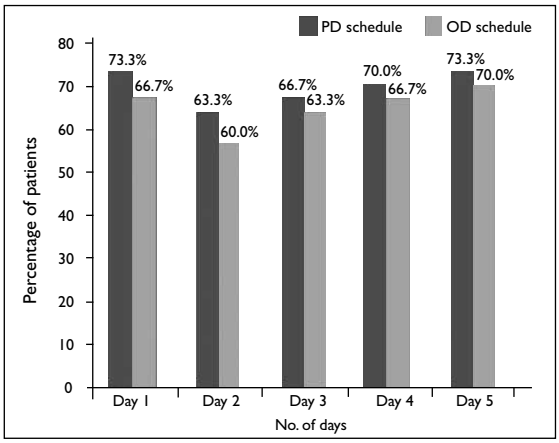

Fig. 3 Graph shows the percentage of nausea-free patients following treatment with palonosetron plus dexamethasone (PD) vs. ondansetron plus dexamethasone (OD).

DISCUSSION

This study was conducted in head and neck cancer patients in order to compare the antiemetic efficacy of ondansetron and palonosetron following a moderately emetogenic cancer chemotherapy. The stimulation of serotonin released from enterochromaffin cells of the gastrointestinal mucosa by chemotherapeutic drugs triggers emesis through the stimulation of the chemoreceptor trigger zone and the vomiting centre in the central nervous system,[13] and 5-HT3 receptor antagonists act as antiemetic agents by their central as well as peripheral action.[14] High-dose glucocorticoids when combined with 5-HT3 receptor antagonists have been found to improve the control of cancer chemotherapy-induced emesis.[15] The mechanism of dexamethasone antiemetic activity is not fully understood, but may involve the ability of steroids to reduce prostanoid synthesis by inhibiting arachidonic acid release, as it has long been known that emesis can be evoked by certain prostaglandins.[16,17]

Palonosetron, a second-generation 5-HT3 receptor antagonist, shows a better response in controlling cancer chemotherapy-induced nausea and vomiting in both the acute (within 24 hours) and delayed (Day 2–5) phases, as compared to the first generation 5-HT3 receptor antagonist, ondansetron.[8,9] Aapro et al reported that complete response of emesis control in the acute phase was numerically higher in the PD schedule compared to the OD schedule (64.7% vs. 55.8%) group.[18] Similar results were obtained in the current study, where complete response in the acute phase was found to be superior in the PD schedule group than the OD schedule group. The responses in the delayed phase in our study tended to be better than those in the study of Aapro et al, who reported complete response of delayed emesis in 42% of patients on a PD schedule and 28.6% of patients on an OD schedule, respectively.[18] The overall complete response to control emesis was slightly better in the PD schedule group than in the OD schedule group in the current study. Similar results were reported from Aapro et al's study,[18] where the overall complete response was observed in 40.7% and 25.2% of patients with a PD schedule and OD schedule, respectively.

The differences in nausea-free rates were numerically higher for the PD group on each day, but not statistically superior, both in our study and in the study by Aapro et al, in which they reported that the greatest magnitude of difference between the two groups was on Day 3, when 49% of PD patients and 38% of OD patients were free from any nausea.[18] However, in our study, the greatest magnitude of difference was on Day 1 and 2, where the nausea-free state was experienced on Day 1 by 73.3% and 66.7% of patients on the PD and OD schedule, respectively, and on Day 2, by 63.3% and 56.7% of PD and OD patients, respectively. According to our study, the failure rate of control of delayed nausea was higher in patients on the OD schedule as compared to those on the PD schedule, thus indicating the superiority of the PD schedule over the OD schedule.

In conclusion, the clinical observations suggest that a PD schedule was slightly better than an OD schedule in controlling cancer chemotherapy-induced nausea and vomiting in the acute as well as delayed phases, although this difference was not statistically significant.

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