ORIGINAL ARTICLE

Ondansetron Against Metoclopramide/ Dexamethasone – A Comparative Study

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Summary

This trial was carried out in Hospital Kuala Lumpur. Fifty-two patients who were scheduled to receive their first or subsequent courses of cancer chemotherapy with single dose cisplatinum containing chemotherapy regimens were evaluated. Thirty-four patients were given ondansetron in one group while 18 in the other group received metoclopramide with dexamethasone.

The response to treatment was categorised as complete (0 emetic episode), major (1 or 2 emetic episodes), minor (3 to 5 emetic episodes) or failure (>5 emetic episodes or rescue medication). Among the 52 patients, a complete or major control (0 to 2 emetic episodes) was achieved in 23/34 patients (68%) from the ondansetron group and in 3/18 patients (17%) from the metoclopramide with dexamethasone group ($p < 0.002$) on day 1. Similarly, the control of nausea was greater in the ondansetron group compared with the metoclopramide with dexamethasone group ($p < 0.0009$) on day 1. Two patients were excluded (dropped out) after day one from each of the two study groups due to excessive vomiting subsequent to cisplatinum therapy. From days 2 to 6, there was a trend in favour of ondansetron. Both treatments were well tolerated. The results of this trial show that in the prophylaxis of nausea and vomiting induced by cisplatinum containing chemotherapy, the efficacy of ondansetron is superior to that of a standard anti-emetic combination, metoclopramide with dexamethasone.

Key Words: Antiemetics, Cisplatinum, Comparative study, Ondansetron

Introduction

Ondansetron is a novel, highly selective 5HT3 antagonist[1] which has been shown to be highly effective in the prophylaxis of nausea and vomiting induced by cisplatinum[2,3] and non-cisplatinum chemotherapy regimens[4,5,6]. It is devoid of the dopamine antagonist activity. It has a half life of the order of three hours and the mean bioavailability of the oral presentation is approximately 60%.

Since the efficacy of ondansetron has been demonstrated, its evaluation in comparison to a metoclopramide-dexamethasone combination, the standard regimen used in Malaysia, was a logical step.

This randomised trial was designed to obtain data on the clinical efficacy and safety of ondansetron as compared to a standard metoclopramide with dexamethasone regimen for the prevention of nausea and vomiting from cisplatinum containing chemotherapy regimens in Malaysia.

Methods

Study design

A randomised, open, comparative, parallel study design was employed to compare ondansetron against a standard metoclopramide with dexamethasone regimen for the prevention of emesis induced by cisplatinum containing chemotherapy regimens.

Patients receiving cisplatinum containing chemotherapy regimens were randomised in a 2:1 (ondansetron: standard regimen) ratio to receive either anti-emetic regimen.

Patients

From January 1991 to June 1991, all adult patients of age 18 years and above scheduled to receive their first or subsequent courses of cancer chemotherapy with single dose cisplatinum containing chemotherapy regimens were included in our study.

Criteria for exclusion from the study before randomisation were: patients receiving cisplatinum on sequential days e.g. as part of the Einhorn regimen; severe concurrent illness other than neoplasia; other causes of vomiting e.g. CNS metastases, gastrointestinal obstruction; patients receiving concurrent medication with benzodiazepines (e.g. lorazepam, diazepam), except when given for night sedation; patients who had received anti-emetic therapy in the first 24 hours prior to chemotherapy; patients who had experienced vomiting in the previous 24 hours and pregnancy.

Blood samples were taken for routine haematology, creatinine, electrolytes and liver function tests (bilirubin, AST, ALT and GGT) prior to the administration of ondansetron or the standard anti-emetic regimen. This study was approved by the ethics committee of the study centre. All patients gave their written consent.

Anti-emetic regimen

Patients were randomly assigned to receive one of the following two anti-emetic regimens in a 2:1 ratio (ondansetron: standard regimen):

Group A: Patients randomised to receive ondansetron. Ondansetron at a dose of 8mg (4ml) as a slow intravenous injection or as an intravenous infusion over 15 minutes, prior to the administration of cisplatin. A continuous intravenous infusion of ondansetron would then be set up to run for 24 hours at a rate of 1mg/hour. Alternatively ondansetron might given as two further 8mg doses as slow intravenous injection four and eight hours after the start of cisplatinum. During days 2-6, the patient received oral medication with ondansetron at a dose of 8mg three times daily. The patients were recommended, where possible, to take each tablet at least one hour before meals.

Group B: Patients randomised to receive standard regimen: metoclopromide with dexamethasone. Patients in this group were given intravenously, metoclopramide 10mg every six hours and dexamethasone 4mg every eight hours for the first 24 hours. Oral metoclopramide at a dose of 10mg every six hours was given starting 24 hours from the first intravenous dose of the drug. This was continued for the following five days up to day six.

Assessment criteria

All patients were hospitalised for at least 24 hours following the start of the cisplatinum infusion. During this period, the timing and number of emetic episodes over the first 24 hours were confirmed with the patient and recorded on the diary cards. For days 2 – 6 (delayed emesis), patients recorded on a diary card provided.

An emetic episode was defined as a single vomit or retch or any number of continuous vomits or retches. Emetic episodes were separated by the absence of vomiting or retching for at least one minute. If a patient totally failed to respond (i.e. experiences > 5 emetic episodes) in the first 24 hours after starting anti-emetic therapy, he or she might have been withdrawn from the study and given rescue medication according to the individual investigator's choice.

The response to treatment was graded as complete (0 emetic episode), major (1 or 2 episodes), minor (3 to 5 episodes) or failure (more than 5 episodes or need for rescue medication). Those patients showing a complete or major response were regrouped into 'success' (0 to 2 episodes). Nausea was recorded according to a graded scale: 0-none; 1-mild (did not

interfere with normal life); 2-moderate (interfered with normal daily life); and 3-severe (patients bedridden because of nausea). Any adverse events observed during and after treatment were recorded by the investigators.

Statistical analysis

Treatment A refers to the group receiving ondansetron, while treatment B refers to the group receiving the standard metoclopramide with dexamethasone regime.

Categorical data were analysed using the Chi-square test. Yates correction was carried out for 2 by 2 contingency tables, while Fisher's exact test was performed in the case of tables having low expected frequency in at least one cell.

Data on nausea and vomiting were analysed separately for day 1 and days 2 to 6. The mean, median and standard deviation were obtained for quantitative data such as number of emetic episodes and maximum intensity of nausea score. The mean values for the experimental groups were tested using the Mann-Whitney U test. A difference is considered to be significant when the P value is equal to or less than 0.05.

Results

A total of 55 patients were identified to take part in the study. Data on 55 patients (37 patients in treatment group A and 18 patients in treatment group B) were analysed and presented. Fifty-two patients were fully evaluated for clinical efficacy. Three patients were excluded because of the presence of nausea in the 24 hours before receiving cisplatinum.

General characteristics of trial subjects

The general characteristics of the patients are presented in Table I. There was statistically no significant difference between the two treatment groups for all the variables shown in this table.

The median age of the patients indicated that those who received treatment A were slightly older. The peak age group of those who received treatment A was between 50-59 years, compared to those who received treatment B. Their peak age group was below 39 years with a minimum of 19 years (Table I).

Though there were slightly more males receiving treatment B there was statistically no significant difference in sex distribution of the patients in the two treatment groups.

The median dose of cisplatinum received by the two groups was similar. Most patients in both groups received cisplatinum dosage that were equal to and more than 90 mg. Again there was statistically no significant difference in the administered dosage patterns for cisplatinum between the two groups.

The pattern of primary tumours among the patients in the two groups was also almost similar. Tumours of the head and neck, and gynaecological tumours involving the cervix and uterus were predominant.

Though the proportion of patients with liver metastasis was higher in those receiving treatment B, the difference was statistically not significant.

None of the patients in either group received cisplatinum alone. Most received cisplatinum and one other chemotherapeutic drug (Table I). Most of those on ondansetron had received 5-FU in addition to cisplatinum. This was also similarly observed for those on treatment B. For those on treatment A, the two additional drugs administered together with cisplatinum were commonly bleomycin and cyclophosphamide. As for those on treatment B, the two additional drugs were commonly bleomycin, cyclophosphamide or adriamycin. In both groups the three additional drugs most often used with cisplatinum were bloemycin, vincristine and methotrexate.

Control of acute emetic episodes on day 1

Three patients receiving treatment A were found to have nausea in the 24 hours before receiving cisplatinum and had to be excluded from the analysis when assessing the clinical efficacy of the drug in protecting the patients from vomiting and nausea. After excluding these three patients, the remaining 52 patients, 34 receiving treatment A and 18 patients receiving treatment B, were subjected to further analysis to assess clinical efficacy of the drugs on trial. The results are presented in Table II.

Complete protection from nausea was seen in 16

Table I
General characteristics of patients

	Treatment A (n = 37)	Treatment B (n = 18)
Age (years):		
median	47.0	42.0
<39	11 (29.7%)	8 (44.5%)
40 - 49	8 (21.6%)	4 (22.2%)
50 - 59	14 (37.8%)	3 (16.7%)
=/> 60	4 (10.8%)	3 (16.7%)
minimum	26.0	19.0
maximum	72.0	69.0
Sex		
males	19 (51.4%)	12 (66.7%)
females	18 (48.6%)	6 (33.3%)
Cisplatinum dosage (mg)		
median	100.00	112.5
<90	4 (10.8%)	1 (5.6%)
=/>90	33 (89.2%)	17 (94.4%)
Primary tumour sites		
head/neck	18 (48.6%)	9 (50.0%)
gynaecological	11 (29.7%)	5 (27.8%)
lung	2 (5.4%)	1 (5.6%)
gastro-intestinal	2 (5.4%)	1 (5.6%)
others	4 (10.8%)	2 (11.1%)
Liver metastasis		
no	33 (89.2%)	12 (66.7%)
yes	4 (10.8%)	6 (33.3%)
Chemotherapy		
Cisplatinum with:		
one other drug	16 (43.2%)	8 (44.4%)
two other drugs	11 (29.7%)	7 (38.9%)
three other drugs	10 (27.0%)	3 (16.7%)

(47.1%) treatment A patients compared to two (11.1%) patients on treatment B, this difference being statistically significant. Complete protection from emesis (vomiting or retching) as defined in the protocol was obtained in 16/34 (47.1%) of those on treatment A compared to only 1/18 (5.6%) on treatment B. The difference was

Table II
Protection from vomiting and nausea, day 1

	Treatment A (n = 34)	Treatment B (n = 18)	p value
No. emetic episodes (mean ± std dev)	1.68 ± 2.7	5.17 ± 3.5	0.0001
Max score of intensity of nausea (mean ± std dev)	0.77 ± 8.6	1.72 ± 0.9	<0.0009
Interval to first vomit (hours) (mean ± std dev)	6.88 ± 8.6	2.18 ± 2.0	n.s
Distribution of emetic episodes: complete protection	16 (47.1%)	1 (5.6%)	<0.007
complete + major response (success)	23 (67.7%)	3 (16.7%)	<0.002
minor response	9 (26.5%)	10 (55.6%)	n.s
failure of treatment	2 (5.9%)	5 (27.8%)	<0.05
Complete protection from nausea	16 (47.1%)	2 (11.1%)	<0.03

statistically significant. A major response for emetic episodes (1-2 emetic episodes) was seen in seven (20.6%) patients on treatment A while this was observed in two (11.1%) who were on treatment B. Hence "success", which included complete protection from emesis and a major response, was observed in 23 (67.7%) patients receiving treatment A compared to only three (16.7%) receiving treatment B. This difference was also statistically significant. A minor response was obtained in nine (26.5%) patients on treatment A compared to ten (55.6%) patients on treatment B, while failure of treatment occurred in two (5.9%) patients on treatment A versus five (27.8%) patients on treatment B.

The mean number of emetic episodes and the mean maximum intensity of nausea score were all less for treatment A compared to treatment B. Both differences were statistically significant.

For treatment A, the mean interval time to the first vomiting episode (6.88 hours) was longer than that for treatment B (2.18 hours). However, this difference was statistically not significant.

Control of delayed emetic episodes and nausea during days 2 to 6

Table III focuses on vomiting and nausea for days 2 to 6. Two patients were removed on day 1 due to excessive vomiting experienced subsequent to cisplatinum therapy. Hence 50 patients were left for analysis of the data pertaining to days 2 to 6.

It can be seen that protection for vomiting was higher for treatment A, the differences being greatest for days two to four. The protection from nausea too was higher for treatment A, with the differences being large on all the days.

The mean number of vomiting episodes and the mean maximum intensity of nausea score during days 2 to 6 were also less for those on ondansetron on all the days.

Table III
Vomiting and nausea, days 2 to 6

	Treatment A (n = 33)	Treatment B (n = 17)	p value
Complete protection from vomiting			
day 2	19 (57.6%)	3 (17.6%)	<0.02
day 3	21 (63.6%)	7 (41.2%)	n.s.
day 4	28 (84.8%)	8 (47.1%)	<0.008
day 5	28 (84.8%)	12 (70.6%)	n.s.
day 6	30 (90.9%)	13 (76.5%)	n.s.
Complete protection from nausea			
day 2	7 (21.2%)	1 (5.9%)	n.s
day 3	9 (27.3%)	1 (5.9%)	n.s
day 4	15 (45.5%)	1 (5.9%)	<0.02
day 5	20 (60.6%)	3 (17.6%)	<0.01
day 6	28 (84.8%)	7 (41.2%)	<0.005
Vomiting episodes (mean ± std dev)			
day 2	1.68 ± 2.7	3.44 ± 3.4	<0.02
day 3	0.81 ± 1.7	1.88 ± 2.5	n.s.
day 4	0.54 ± 1.7	1.56 ± 2.3	<0.01
day 5	0.46 ± 1.7	1.11 ± 2.3	n.s.
day 6	0.30 ± 1.7	0.83 ± 2.2	n.s.
Intensity of nausea score (mean ± std dev)			
day 2	1.81 ± 2.3	2.39 ± 2.5	n.s.
day 3	1.32 ± 1.9	2.28 ± 2.6	<0.05
day 4	1.02 ± 2.0	2.06 ± 2.6	<0.01
day 5	0.87 ± 2.1	1.67 ± 2.7	<0.02
day 6	0.60 ± 2.7	1.44 ± 2.8	<0.01

Adverse reactions

No adverse reactions were found in patients of the two treatment groups.

Discussion

Various anti-emetic regimens incorporating metoclopramide, dexamethasone, diphenhydramine or lorazepam have been shown to be effective in the prevention of immediate emesis and nausea following cisplatinum chemotherapy. However, even with these regimens a proportion of patients are not completely protected and troublesome extrapyramidal reactions can develop[7-9].

This study showed that ondansetron is significantly

better than a combination of metoclopramide with dexamethasone in controlling acute emesis and nausea associated with cisplatinum containing chemotherapy regimens.

'Success' in control of emesis was improved from 16.7% for patients on standard regimen of metoclopramide with dexamethasone (treatment B), to 67.7% for patients given ondansetron (treatment A). Table I shows that there was statistically no significant difference between the two treatment groups for the general characteristics of trial subjects. This suggests that the randomisation to the two groups was successful and the two treatment groups were statistically comparable. In view of that, differences in efficacy between the two regimens were clearly due to anti-emetic treatment and not to an imbalance in prognostic factors that might influence the development and control of emesis[10].

Cisplatinum may evoke both an acute emetic response during the first 24 hours following treatment and a less well-recognised syndrome of delayed emesis. While delayed emesis is usually less severe in terms of frequency of vomiting episodes, the problem continues to result in significant morbidity[11]. The superiority of ondansetron over the standard regimen on day 2 and 4 confirmed the results noted for complete protection from delayed vomiting[12]. However, in the present trial, the result from days 3, 5 and 6 were less demonstrative, although there was a trend in favour of ondansetron on each day. The fading action of the cytotoxic drugs has also resulted in a decreasing emetic risk from one day to the next for both treatment groups.

The two groups tolerated anti-emetic treatment well and the absence of adverse events to anti-emetic therapy could be due to the small number of patients in the study.

In this study, ondansetron was given as continuous infusion or intermittent doses after the initial dose. However, preliminary data showed that a single 8mg or 32mg intravenous dose, given before chemotherapy, is as effective as intermittent dosing schedules or constant infusion[13, 14].

In conclusion, the efficacy of ondansetron is superior to that of a recognised anti-emetic combination, metoclopramide with dexamethasone. Despite the encouraging results, a substantial number of patients still had some nausea or vomiting. Since there are few conditions for which treatment is 100% effective, any clinician with imagination will be always on a look-out for potential improvements in therapy. The aim of ensuring a complete control in a still larger number of patients has been shown using the combination of ondansetron with dexamethasone[15].

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