Thai Journal of Obstetrics and Gynaecology
March 2002, Vol. 14, pp. 51-58

GYNAECOLOGY

A Randomized, Double Blinded Comparison of Single Dose Ondansetron and Metoclopramide Plus Dexamethasone in The Prevention of Single Agent Carboplatin Induced Emesis in Ovarian and Endometrial Carcinoma

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ABSTRACT

Objective To compare the efficacy of ondansetron and metoclopramide plus dexamethasone in preventing emesis induced by single agent carboplatin within 24 hours.

Design Randomized, double-blinded, crossover trial.

Settings Gynecologic Oncology unit at King Chulalongkorn Memorial Hospital.

Patients Patients with ovarian and endometrial carcinoma being treated in gynecologic on cology unit with postoperative adjuvant carboplatin. Of 72 patients, 67 patients were evaluated for crossover analysis, 5 were excluded due to failure to get the second crossover-courses. (3 patients-loss to follow up, 2 patients-discontinued chemotherapy because of progressive disease, another with wrong pathological report (borderline mucinous cystadenoma)

Interventions All patients received carboplatin 350mg/m^2 body surface area and ondansetron 8 mg or metoclopramide 20 mg plus dexamethasone 20 mg in a crossover style. Both antiemetic regimens were given intravenously 30 minutes prior to carboplatin infusion.

Measurements and main results Within 24 hours after receiving carboplatin, complete control was seen in 67.1% of the ondansetron-treated patients and 43.5% of the metoclopramide and dexamethasone-treated patients ($P<0.05$), major control was seen in 81.4% of the ondansetron-treated patients and 68.1% of the metoclopramide and dexamethasone-treated patients. ($P>0.05$)

Conclusions Single dose ondansetron was more effective than metoclopramide plus dexamethasone in preventing acute emesis induced by single agent carboplatin. The emetic control was less if ondansetron was given on second cycle.

Key words: carboplatin, antiemesis, ondansetron, metoclopramide plus dexamethasone, ovarian carcinoma, endometrial carcinoma.

Chemotherapy induced emesis is an important clinical problem that lead to patient's intolerance and discontinuation of treatments. In the treatments of gynecologic malignancies, despite of its highest emetogenic property, cisplatin alone or cisplatin-based chemotherapeutic agents were the most widely

used first line drugs. Growing concern on patient tolerance and the avoidable emetogenic side effect leaded to more use of its sister drug, carboplatin which is closely related to cisplatin and proven to share the same efficacy but less emetic properties (moderate emetogenic potential).[1-3] Although carboplatin is significantly less emetogenic than cisplatin, most patients still experience nausea and or vomiting if no prophylactic antiemesis is given.[4] Several kinds of antiemetic drugs were used to prevent its emesis, however, 40% of the patients still had emesis.[5] Metoclopramide with or without dexamethasone combined with sedative drugs were conventionally used but it had low efficacy with many adverse effect especially extrapyramidal effect and sedative effect.

Ondansetron, a selective serotonin receptor antagonist is a potent antiemetic agent. These agents have shown greater antiemetic efficacy than metoclopramide with or without dexamethasone in many studies.[6-17] Standard regimen for ondansetron was 0.15mg/kg intravenously every 4 hours for 3 doses. Hainsworth18 found that intravenous single 8 mg dose of ondansetron was effective as the standard regimen and convenient for patients receiving chemotherapy in an outpatient setting.[18-19] However, most study reports compared in only cisplatin treated patients with variety in type of tumor and dose of cisplatin. Since carboplatin is currently more common used in our hospital, it is our intention to explore the suitable antiemetic drugs for carboplatin treated patients.

In our randomized, double blinded, crossover study, aims to compare the efficacy of single dose ondansetron with single dose metoclopramide plus dexamethasone in the prevention of emesis within 24 hours which was induced by single agent carboplatin at the same dose in early ovarian cancer or endometrial cancer patients.

Materials and Methods

Patients : From September 1999 to May 2001, 72 patients with pathologically confirmed of early staged of ovarian or endometrial carcinoma were enrolled into the study. Eligible patients were those who had received no prior chemotherapy and had Karnofsky score over 80 percent. Exclusion criteria were those who had vomiting or previously used of antiemetic drugs within the 24 hours before starting chemotherapy, impaired renal function as defined by serum creatinine value more than 2.0 mg/dl or creatinine clearance less than 50 ml/min, received radiation therapy to the abdominal or pelvic region within 48 hours before or during study, had evidence of brain metastasis, bowel obstruction or any other serious concurrent illness.

Approval for the study was obtained from the Ethical Committees of Chulalongkorn University. Patients were given informed consent before the start of the study.

Chemotherapy treatment

All patients received carboplatin in a dose of 350 mg/m2 of body surface area, dissolved in 500 ml of 5 percent dextrose in water and administered as a 4 hours intravenous infusion.

Antiemetic treatment

Patients were randomized by block of four to receive one of the following two antiemetic treatment regimens.

Treatment A : Ondansetron (Zetron®) 8 mg (4ml) added in normal saline 4 ml and given intravenously 30 minutes prior to carboplatin infusion.

Treatment B : Metoclopramide 20 mg (5mg/ml) added with dexamethasone 20 mg (5mg/ml) given intravenously 30 minutes prior to carboplatin infusion.

Patients were randomized to receive either treatment A or B for their first course of chemotherapy and then were crossed over to the other antiemetic treatment for their second courses after 4 weeks while the dose of carboplatin was kept unchanged.

After carboplatin infusion, they would received additional metoclopramide 10 mg orally if they had experience of emesis for every 6 hours. But if they could not eat or had severe emesis, they would

receive metoclopramide 10 mg intravenously.

Assessment of response

Patients were assigned and observed for nausea, vomiting and other adverse effects for the first 24 hours after carboplatin infusion. The primary efficacy variable was the number of emetic episode (EE). A single emetic episode was defined as any vomiting that produced any stomach contents through the mouth or any number of continuous vomits that occurred within 1 minute of each other. Emetic episodes was separated from each other by the absence of vomiting for at least 1 minute.[13] The secondary efficacy variable was the degree of patient nausea. Nausea was recorded according to a 11-graded scale (0, no nausea ; 1-3 score, mild nausea ; 4-7 score,moderate nausea ; 8-10 score, severe nausea).[16]

Emetic control was graded as complete control (no EE and no nausea), major control (0-1 EE and/or mild degree of nausea), no response (more than 1EE and/or moderate to severe degree of nausea).

After the second course of treatment, patients were asked to indicate which antiemetic treatment regimen they preferred.

Statistical analysis

The Student's t-test was used to compare the ondansetron and metoclopramide with dexamethasone groups in respect to age, parity, weight, height and Chi-square for comparison to type of primary tumor. The emetic control between 2 groups were analyzed by Mcnemar Chi-square. The number of emetic episodes, time between carboplatin therapy to the first emetic episode was analyzed by pair t - test and nausea grading was analyzed by Wilcoxon rank sums test. Adverse effect and patient's preference were compared by Chi-square test. P values less than 0.05 were regarded as statistically significant.

Results

72 patients were enrolled into this study. Characteristics of the patients were shown in table 1. There were no statistically significant differences between two groups

Table 1. Patient characteristics

Characteristics	Treatment A (n = 36)	Treatment B (n = 36)
Mean age (years)	50.5±8.7	49.8±9.1
Parity	1.1±1.7	1.5±1.8
Mean weight (kilograms)	53.8±10.5	52.4±11.5
Mean height (centimeters)	154.4±5.5	154.4±5.3
Primary tumors (%)		
Ovarian carcinoma	22 (61.1%)	27 (75%)
Endometrial carcinoma	14 (38.9%)	9 (25%)

Five patients were not evaluable in the cross-over analysis because they did not received second course : 3 patients - loss to follow up ; 1 patient - treatment was changed due to progressive disease ;1 patient - discontinuation of the treatment due to pathological report revision as borderline mucinous cystadenoma and deleted from the study. (3 patients were in treatment A and 2 patients were in treatment B).

The efficacy of ondansetron and metoclopramide plus dexamethasone in the control of emesis within 24 hours was shown in table 2 and 3. Complete

control was seen in 67.1% for ondansetron and 43.5% for metoclopramide plus dexamethasone. The difference was statistically significant (P<0.05). But there was no significant difference in major control between both groups (81.4% and 68.1 %, P=0.057).

If we analyzed the outcome according to the sequence of antiemetic agent, we found that complete control in ondansetron group was higher than in metoclopramide with dexamethsone group but the statistical significance was observed only when ondansetron was given on the first course of chemotherapy. However, major control and no response were no statistical significance between both sequences. (Table 3 and figure 1,2)

Table 2. Emetic control

	Ondansetron (n = 70)	**Metoclopramide plus dexamethasone (n = 69)**	**P value**
Complete control	47 (67.1%)	30 (43.5%)	P<0.05
Major control	57 (81.4%)	47 (68.1%)	NS
No response	13 (18.6%)	22 (31.9%)	NS
Numbers of EE (mean±SD)	0.5±2.1	1.8±4.0	P<0.05
Nausea score (mean±SD)	1.4±2.5	2.4±2.8	P<0.05
Time to first EE (mean±SD)	16.2±5.6	10.9±4.5	NS

Table 3. Distribution of emetic control by sequence group

Sequence group	**Complete control**	**Major response**	**No response**
Ondansetron then metoclopramide with dexamethasone			
course 1 (n=36)	29 (80.6%)*	32 (88.9%)	4 (11.1%)
course 2 (n=33)	11 (33.3%)*	23 (69.7%)	10 (30.3%)
Metoclopramide with dexamethasone then ondansetron			
course 1 (n=36)	19 (52.8%)	24 (66.7%)	12 (33.3%)
course 2 (n=34)	18 (52.9%)	25 (73.5%)	9 (26.5%)

* P value < 0.05

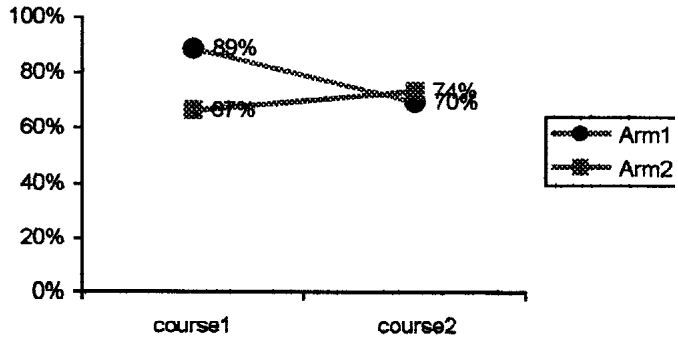

Fig1. Complete control according to sequence of the antiemetic treatment.

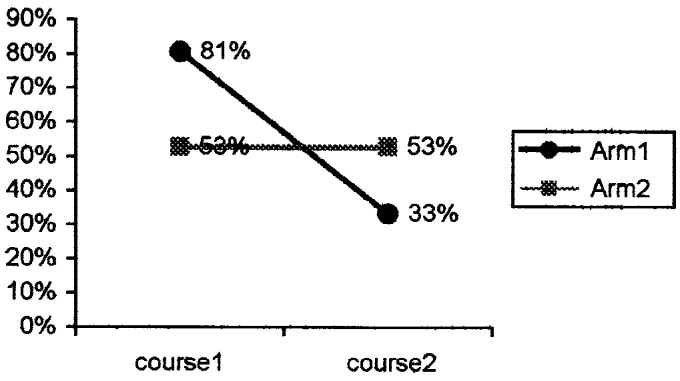

Fig.2. Major control according to sequence of the antiemetic treatment.

12 patients who were given ondansetron had emetic episode compared with 29 patients who were given metoclopramide plus dexamethasone. Mean time to first emetic episode in ondansetron treated group was longer than metoclopramide plus dexamethasone treated group but no statistical significance (16.2/10.9 hours). Nausea grade and number of emetic episodes found in ondansetron treated group were less than metoclopramide plus dexamethasone.($P<0.05$) No statistical significant difference between both groups in requiring antiemetic rescue treatment. And only 2 patients in metoclopramide with dexamethasone group (in the sequence that metoclopramide plus dexamethasone was given first) required intravenous metoclopramide.

Of the 33 patients given ondansetron first, 17(52%) preferred ondansetron, 3(9%) preferred metoclopramide plus dexamethasone , and 13(39%) expressed no preferences. Of the 34 patients given metoclopramide plus dexamethasone first, 10 (29%) preferred ondansetron, 5(15%) preferred metoclopramide plus dexamethasone , and 19 (55%) expressed no preferences. The overall preference was 40% for ondansetron, 12% for metoclopramide plus dexamethasone, and 48%

expressed no difference. (Table 4)

Table 4. Patient's preference, according to sequence of antiemetic treatment

Sequence	Agent prefered			
	Ondansetron	Metoclopramide plus dexamethasone	No difference	Total
Treatment A	17 (52%)	3 (9%)	13 (39%)	33
Treatment B	10 (29%)	5 (15%)	19 (56%)	34
Total	27 (40%)	8 (12%)	32 (48%)	67

Treatment A = Ondansetron then metoclopramide plus dexamethasone

Treatment B = Metoclopramide plus dexamethasone then ondansetron

Headache or dizziness was the most common adverse effect during both groups (28.6% for ondansetron and 26.1% for metoclopramide plus dexamethasone) and other adverse effects were not statistical significant difference. In this study, no extrapyramidal symptom was observed. (Table5)

Table 5. Adverse effects

Events	Ondansetron(n=70)	Metoclopramide and dexamethasone(n=69)
Headache	20 (28.6%)	18 (26.1%)
Constipation	2 (2.9%)	0
Diarrhea	11 (1.4%)	0
Dyspepsia	1 (1.4%)	0
Sedation	3 (4.3%)	3 (4.3%)
Insomnia	6 (8.5%)	3 (4.3%)
Total	33 (47.1%)	24 (34.7%)

Discussion

Although carboplatin is significantly less emetogenetic than cisplatin, more than 80% of patients experienced nausea and vomiting if they did not receive any prophylactic antiemetic agents[20] while 40% still did so despite being given any antiemetic agents.[5] It is our intention to compare single prophylactic dose 8 mg of ondansetron and single dose 20 mg of metoclopramide plus 20 mg of dexamethasone in a randomized, double blind, crossover fashion. Ondansetron had long been proven to be superior in controlling of nausea and vomiting induced by carboplatin-containing chemotherapy within 24 hours in a variety of patient characteristics. All patients enrolled in this prospective study were very selective, in which only patients with apparent early ovarian or endometrial cancer who had no pelvic or abdominal extension. A single agent carboplatin at the same dose was used as a crossover design, in order to reduce interpatient variablility. This selection was aimed to compare the two antiemetic drugs for carboplatin only in a unique patient group. The strength of our report is that single agent carboplatin at the same dose was used and our patients carried no tumor burden since all of them were in apparent early stage and all macroscopic tumor were removed.

In our study, complete control in ondansetron group was significantly more than in metoclopramide plus dexamethasone group (67%/43%). But if we analyzed the outcome according to the sequence of the antiemetic agent, complete control in ondansetron group was statistical significant superior than metoclopramide plus dexamethasone group only in the sequence when ondansetron was given in first order (80.6%/33.3%, P<0.05). If ondansetron was given as the second order, its antiemetic effect was lower and was not differed from metoclopramide plus dexamethasone group (52.9%/52.8%). Because washout period in this study was 4 weeks, the carryover effect should not happen. This phenomenon might be explained by psychogenic or anticipatory effect.

Number of patients that had emetic episode in ondansetron group were less than in metoclopramide with dexamethasone group (12/29 patients). Mean time to first EE in ondansetron group was longer than in metoclopramide with dexamethason group but had no statistically significant difference. Although nausea score and number of emetic episodes in ondansetron group was significant less than in metoclopramide with dexamethasone group, but most patients had only mild grade of nausea score and had less than 2 episodes of emesis.

The most common adverse effects observed in both groups were headache (28%/26%) which had no statistically significant difference. In our study, we did not found any extrapyramidal effect, which was in agreement with report from Cubeddu that this extrapyramidal effect was commonly seen in young patients especially less than 30 years old and among who receive high dose metoclopramide.[7]

Although metoclopramide plus dexamethasone seem to be inferior than ondansetron but still conferred therapeutic success in many patients (68%) with few adverse effects and less costly than ondansetron. If cost-effectiveness is considered as a major factor, metoclopramide with dexamethasone can be used as first-line for prevention of carboplatin induced emesis. Tasavaris et al.21 used ondansetron only in the first course and if the patients had not emesis or had only mild degree of nausea, metoclopramide with methylprednisolone would be given in another course. But if severe vomiting were occurred, ondansetron with methylprednisolone would be used as an anti-emetic agent. They found that in the first course 79% of patients had mild or no vomiting and 57% of patients success with metoclopramide and methylprednisolone after complete treatments. They concluded that if we administered ondansetron only in patients who needed it, the overall cost would decrease to 44%.[21]

From our study, we found that ondansetron 8 mg intravenously injection before carboplatin infusion at least 30 minutes are effective in prevention of emesis within 24 hours. Moreover, single dose of intravenous ondansetron was convenient in outpatient cases. Major drawback in our study is that the period observed for emetic control was truly first 24 hours after carboplatin infusion, this could not refer to protection of nausea and vomiting in delayed phase. However, carboplatin induced emesis usually developed within the first 6-12 hours and largely resolved by 24 hours.[22-23]

Further study should be done in order to prove the optimal dosage and schedule of ondansetron alone or combination with other drugs which will result in further improvement of antiemetic efficacy in acute and delayed carboplatin-induced emesis. Especially delayed emesis, which is still a major problem of carboplatin treatment.[5]

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