Antiemetic Effect of Ondansetron and Dexamethasone in Gynecologic Malignant Patients Receiving Chemotherapy

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Objectives: *To evaluate the antiemetic effect of a single dose of ondansetron and dexamethasone as a prophylaxis for chemotherapy induced acute nausea and emesis and factors associated with the control of acute nausea and emesis.*

Material and Method: *Patients who received single dose of 8 mg ondansetron and 20 mg dexamethasone as a prophylaxis for chemotherapy induced nausea and emesis at Department of Obstetrics and Gynecology, Bangkok Metropolitan Administration Medical College and Vajira Hospital, between October 2004 and April 2006 were identified. The assessment record of the drug efficacy had been evaluated in the first 24 hours after the start of chemotherapy in terms of control of vomiting, and nausea. Age of the patients, history of alcohol intake, type of cancer, regimen of chemotherapy and course of chemotherapy were analysed as possible factors associated with the control of nausea and emesis.*

Results: *Seventy-eight gynecologic-cancer patients receiving 353 cycles of chemotherapy were evaluated in this study. Completed control of acute vomiting and nausea were 68% and 57.2% respectively. Complete control of acute vomiting and nausea were 56.9% and 45.4% in patients of ≤ 45 years compared to 78.8% and 68.7% in those with > 45 years. Complete control of acute vomiting and nausea were 59.2% and 48.7% in those receiving cisplatin-containing regimens compared to 86.7% and 75.2% in non-cisplatin containing regimens. Univariable and multivariable analysis showed that younger patients and those who received cisplatin-containing regimens had significant lower rates of complete control of both nausea and emesis. Patients receiving the first three courses of chemotherapy had significantly higher rate of complete control of nausea but not emesis as compared to those receiving chemotherapy after the third course.*

Conclusion: *A single intravenous dose of 8 mg of ondansetron and 20 mg of dexamethasone had good control of acute nausea and vomiting only in those who received non-cisplatin containing regimens and those older than 45 years.*

Keywords: *Chemotherapy induced emesis, Ondansetron, Dexamethasone, Cisplatin, Age*

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Uncontrolled nausea and vomiting in patients receiving chemotherapy frequently result in poor nutritional intake, metabolic derangement, deterioration of physical and mental conditions, as well as a negative impression and eventual rejection to receive further chemotherapy[1-3].

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Progress has been made in preventing acute nausea and vomiting (occurring within 24 hours of chemotherapy)[4-6]. During 1980s, high-dose metoclopramide was demonstrated to improve the control of chemotherapy-induced emesis considerably and has been the cornerstone of effective antiemetic combination[7]. However, it can induce extrapyramidal reactions especially in adolescents, and this remains a major drawback[7-9].

Specific 5-HT_3 receptor antagonists are agents that effectively prevent chemotherapy or radiotherapy-

induced emesis, well tolerated with fewer side effects including headache, constipation, drowsiness, insomnia[4,5,9]. Hence, they become the first-line antiemetic prophylaxis in cancer patients receiving chemotherapy[4-6,10]. Moreover, the efficacy of these agents is further enhanced by the addition of a corticosteroid[11-14]. In our country, ondansetron is one of the 5-HT3 receptor antagonists that were widely used as an antiemetic for chemotherapy induced emesis.

Concerning the dose and schedule of ondansetron, many studies showed that single intravenous dose of ondansetron is as effective as multiple doses or continuous infusion[15-18]. Although, some studies show that higher doses of 32 mg ondansetron gained higher efficacy than single 8 mg dosage[15], other studies reported that a single, higher doses of 12 mg, 24 mg and 32 mg had no significant better efficacy than the 8 mg dose[16,19]. Thus a single 8 mg dose of ondansetron in combination with 20 mg dexamethasone was recommended as standard prophylactic antiemetics for acute phase of chemotherapy induced emesis from highly and moderately high emetogenic chemotherapy in clinical practice guidelines[6,10]. In our institution, single-dose of 8 mg ondansetron, in stead of metoclopramide, in combination with 20 mg dexamethasone were given as standard prophylactic antiemetics for highly and moderately-high emetogenic chemotherapy since October 2004. Our objective is to evaluate the controls of acute emesis, and nausea and factors that may be associated with the complete or incomplete control of acute chemotherapy induced emesis from a single-dose of 8 mg ondansetron with 20 mg dexamethasone.

Material and Method

This study was conducted after the approval from the Ethics Committees of our institution. The patients who received chemotherapeutic agents at the Gynecologic Oncology Unit, Department of Obstetrics and Gynecology, Bangkok Metropolitan Administration Medical College and Vajira Hospital, between October 2004 and April 2006 were identified. Patients were eligible for enrolment if a single intravenous dose of 8 mg of ondansetron and 20 mg of dexamethasone were given prior to chemotherapy. The criteria for exclusion were the presence of nausea and vomiting and the use of antiemetics within 24 hours before the start of chemotherapy, clinical evidence of hepatic dysfunction, use of corticosteroids, unless as physiologic supplementation or as part of the chemotherapy regimen, and use of benzodiazepines, except as night sedation. Brief demographic details, history of alcohol consumption, and history of motion sickness were also recorded.

Routinely in the Gynecologic Oncology Unit, assessment of nausea and vomiting were evaluated during admission based on the number of emetic episodes and the intensity of nausea. Emesis and nausea occurring within 24 hours after the start of chemotherapy were defined as acute phase of chemotherapy induced emesis. An emetic episode was defined as a single vomit or retch or any number of continuous vomits or retches. Emetic episodes had to be separated from each other by the absence of vomiting or retching for at least 5 minutes. The absence of emesis was defined as complete control while presence of any emesis was defined as incomplete control and was subclassified as the following: one or two episodes as major control, three to five episodes as minor control, and more than five episodes as failure of treatment. Nausea was recorded and graded according to the interference with daily life activity: no (complete control of nausea), mild (did not interfere with normal daily life), moderate (interfered with normal daily life), severe (bedridden due to nausea). The duration from beginning of chemotherapeutic drug to first emesis and to first feeling of nausea were also recorded.

Data were analysed by parametric and non-parametric statistics using SPSS statistical software version 11.5 (Chicago, IL). Descriptive statistics were used for demographic data and summarized as mean with standard deviation (SD) or median with range. Categorized variables were compared with the Chi-squared test or Fisher's exact test as appropriate. Multiple logistic regressions were used to identify the independent prognostic factors associated with the complete control of nausea and vomiting. A p-value ≤ 0.05 was considered statistical significance.

Results

Seventy-eight gynecologic-cancer patients receiving 353 cycles of chemotherapy were evaluated in this study. Mean age of the patients was 46.0 ± 11.4 years. The distribution of diseases was ovarian cancer 61 cases (78.2%), cervical cancer 13 cases (16.7%), uterine cancer 3 cases (3.8%), and fallopian tube cancer 1 case (2.6%). Most of the patients (91%) were chemotherapy-naive, while 2 patients (1.3%) had one previous regimen and 5 patients (6.4%) had two or more than two previous regimens of chemotherapy. Only a few patients had history of alcohol intake (2.6%), and none had history of motion sickness. Each patient was evaluated for control of emesis from 1 or 2 regimens of chemotherapy,

and altogether for 1-9 courses of her chemotherapy (median of 3 courses).

The types of chemotherapy given were either cisplatin containing regimens (dosage of 50-75 mg/m^2) or carboplatin combination regimen (dosage of AUC 5-6). Details of chemotherapy are show in Table 1.

Of 353 courses, there were 240 courses (68.0%) of complete control of acute emesis. Major and minor control was achieved in 73 courses (20.7%), and 36 courses (10.2%) respectively while failure of emetic control was found in 4 courses (1.1%). In those who vomited, the median number of vomiting was 2 times (range, 1 to 10 times). The median time from start chemotherapy to first vomiting episode was 10.3 hours (range, 1.0 to 22.3 hours).

The control of acute nausea was as followed; no nausea 202 courses (57.2%), mild nausea 90 courses

Table 1. Type of chemotherapy (n = 353)

Type of chemotherapy	Number	%
Regimen with cisplatin		
cisplatin+cyclophosphamide	188	53.3
cisplatin+etoposide+bleomycin	16	4.5
cisplatin+etoposide	14	4.0
cisplatin+5FU	7	2.0
cisplatin+gemcitabine	6	1.7
cisplatin only	5	1.4
cisplatin+ifosfamide	4	1.1
Regimen without cisplatin		
paclitaxel+carboplatin	82	23.2
carboplatin+cyclophosphamide	24	6.8
carboplatin only	7	2.0

Table 2. Association between patients characteristics,diseases, type/course of chemotherapy and control of vomiting in acute phase (n = 353)

Characteristics	Control of acute vomiting (%)				
	Complete control	Incomplete control			p-value*
		Major control	Minor control	No control	
Age (years)					<0.0001
≤ 45 (n = 174)	56.9	28.2	13.2	1.7	
> 45 (n = 179)	78.8	13.4	7.3	0.5	
History of alcohol intake					1.000
No history (n = 343)	67.9	20.7	10.2	1.2	
Ocassionally intake (n = 10)	70.0	20.0	10.0	0.0	
Type of cancer					0.783
Ovary (n = 290)	67.2	21.4	11.0	0.4	
Cervix (n = 42)	64.3	21.4	9.5	4.8	
Uterus (n = 16)	93.7	0.0	0.0	6.3	
Fallopian tube (n = 5)	60.0	40.0	0.0	0.0	
Type of chemotherapy					<0.0001
With cisplatin (n = 240)	59.2	26.2	13.8	0.8	
Without cisplatn (n = 113)	86.7	8.8	2.7	1.8	
Course of chemotherapy					0.549
First 3 courses (n = 208)	69.2	21.6	8.7	0.5	
More than 3 courses (n = 145)	66.2	19.3	12.4	2.1	
Type of chemotherapy related age					
With cisplatin					0.002
Age ≤ 45 years (n = 131)	50.4	33.6	15.2	0.8	
Age > 45 years (n = 109)	69.7	17.5	11.9	0.9	
Without cisplatn					0.014
Age ≤ 45 years (n = 43)	76.7	11.6	7.0	4.7	
Age > 45 years (n = 70)	92.9	7.1	0	0	

* p-value by chi-square compared between complete control and incomplete control of acute vomiting

(25.5%), moderate nausea 55 courses (15.6%), and severe nausea 6 courses (1.7%). In those who experienced nausea, the median time from start of chemotherapy to the first feeling of nausea was 10.3 hours (range, 1.0 to 22.3 hours).

Age of the patients, history of alcohol intake, type of cancer, regimen of chemotherapy, and course of chemotherapy were analysed as possible factors associated with the control of nausea and emesis from single dose of ondansetron in combination with dexamethasone. In univariable analysis, Table 2 and 3 demonstrated that younger patients (age ≤ 45 years) and those who received cisplatin containing regimens had significant lower rate of complete control of emesis than the corresponding groups. Significant differences in rates of complete nausea control were found in these two groups of patients. Subgroup analysis also showed that complete control of vomiting was significantly higher in patients of > 45 years as compared to younger patients, both in cisplatin and non-cisplatin containing regimens. Complete control of nausea was significantly higher in patients of > 45 years as compared to younger patients in cisplatin containing regimens, and of borderline significance in non-cisplatin containing regimens (Table 2, 3).

Patients receiving the first three courses of chemotherapy had a significantly higher rate of complete control of nausea, though they did not have different control of emesis as compared with those who received ≥ 4 courses of chemotherapy. Type of cancer and history of alcohol intake had no association with control of nausea and emesis in this study (Table 2, 3).

In multivariable analysis, age (≤ 45 years versus > 45 years) and chemotherapeutic agents (cisplatin versus non-cisplatin containing regimens) were independently associated with the complete control of

Table 3. Association between patients characteristics,diseases, type /course of chemotherapy and control of nausea in acute phase (n = 353)

Characteristics	Control of acute nausea (%)				
	Complete control	Incomplete control			p-value*
	no	mild	moderate	severe	
Age (years)					<0.0001
≤ 45 (n = 174)	45.4	32.2	20.1	2.3	
> 45 (n = 179)	68.7	19.0	11.2	1.1	
History of alcohol intake					0.750
No history (n = 343)	57.4	25.1	15.7	1.8	
Ocassionally intake (n = 10)	50.0	40.0	10.0	0.0	
Type of cancer					0.659
Ovary (n = 290)	55.5	27.6	15.9	1.0	
Cervix (n = 42)	57.2	19.0	19.0	4.8	
Uterus (n = 16)	93.7	0.0	0.0	6.3	
Fallopian tube (n = 5)	40.0	40.0	20.0	0.0	
Type of chemotherapy					<0.0001
With cisplatin (n = 240)	48.7	29.6	20.0	1.7	
Without cisplatn (n = 113)	75.2	16.8	6.2	1.8	
Course of chemotherapy					0.029
First 3 courses (n = 208)	62.0	22.1	15.4	0.5	
More than 3 courses (n = 145)	50.4	30.3	15.9	3.4	
Type of chemotherapy related age					
With cisplatin					0.001
Age ≤ 45 years (n = 131)	38.9	36.7	22.9	1.5	
Age > 45 years (n = 109)	60.6	21.1	16.5	1.8	
Without cisplatn					0.051
Age ≤ 45 years (n = 43)	65.1	18.6	11.6	4.7	
Age > 45 years (n = 70)	81.4	15.7	2.9	0	

* p-value by chi-square compared between complete control and incomplete control of acute nausea

Table 4. Side effects of treatment (n = 353)

Side effects	N	%
No side effect	237	67.1
Constipation	92	26.1
Insomnia	50	14.1
Drowsiness	21	5.9
Diarrhea	11	3.1
Headache	9	2.5
Courses with one side effect	72	20.4
Courses with two side effects	21	5.9
Courses with three side effects	23	6.5

vomiting ($p < 0.0001$ for both factors) while age, chemotherapeutic agents and courses of chemotherapy given were independently associated with the complete control of nausea ($p < 0.0001$, < 0.0001 and $= 0.029$ respectively).

Table 4 shows side effects of treatment. Most of the patients had no side effects (67.1%). Among those patients who experienced side effects, the most common of which was constipation (26.1%). These side effects were generally mild to moderate in severity. Complete recovery occurred with conservative treatment.

Discussion

Chemotherapeutic agents are classified into five groups according to their emetic potential. Level 5 (highly emetogenic) agents are extremely emetogenic, from which nearly all patients (> 90%) are expected to vomit. Level 4 (moderately high emetogenic) agents produce emesis in 60-90% of patients. Level 3 agents are moderately emetogenic with 30-60% of patients experiencing emesis. Level 2 (mild emetogenic) agents cause emesis in 10-30% of patients, while level 1 agents are considered non-emetogenic with a less than 10% incidence of emesis[20]. Standard antiemetic prophylaxis for level 3-5 chemotherapeutic agents are single doses of 5-HT3 receptor antagonist in combination with single dose dexamethasone[6,10].

In our institution, a single dose of 8 mg ondansetron in combination with 20 mg of dexamethasone were used as standard antiemetics for level 3 to level 5 chemotherapeutic agents. Level 3-5 chemotherapeutic agents, which were commonly used for gynecologic malignancies are cisplatin (level 5), carboplatin (level 4), cyclophosphamide (level 4), doxorubicin (level 3), epirubicin (level 3) and ifosfamide (level 3). From 353 courses of chemotherapy in this study; 240 courses (68%) were cisplatin containing regimens (level 5), the rest (113 courses) were non-cisplatin containing regimens, all of which contained carboplatin (level 4).

Nausea and vomiting that occur within 24 hours of chemotherapy administration are classified as acute emesis. The overall complete control of acute emesis was 68% and overall control of acute nausea was 57.2%. As expected, the type of chemotherapy is the most significant factors associated with control of both nausea and vomiting. Complete control of vomiting and nausea were achieved in 59.2% and 48.7% in cisplatin-containing regimens compared to 86.7% and 75.2% in non-cisplatin containing regimens. These figures showed that a single dose of 8 mg ondansetron in combination with 20 mg of dexamethasone provided a satisfactory protective effect against nausea and vomiting from non-cisplatin containing regimens or level 3-4 chemotherapeutic agents. Other study of moderately high and moderately emetogenic chemotherapy also reported the complete control of vomiting from a single dose of 8 mg ondansetron in combination with 20 mg of dexamethasone in 77-88%[19].

However, for cisplatin containing regimens or level 5 chemotherapeutic agents, the protective effect against nausea and vomiting was less than satisfactory, the complete control of vomiting and nausea were 59.2 and 48.7% respectively. These results was lower than those from the report of Pectasides et al in which the complete control of vomiting and nausea from the same dose of ondansetron and dexamethasone were 68.8% and 60.5% respectively in patients receiving cisplatin > 80 mg/m^2[21]. Although many studies showed that single higher dose of ondansetron, or multiple doses, or continuous infusion of ondansetron did not provide superior protective effects over single 8 mg dosage[16-20], Hainsworth et al reported that 32 mg of ondansetron provided better control of nausea and vomiting[15]. Manusirivithaya et al showed that complete control of vomiting and nausea from the 2 doses of 8 mg ondansetron and 20 mg of dexamethasone in patients receiving cisplatin of 60 mg/m^2 yielded much better control than in our study which involved only single doses of 8 mg ondansetron, 90% and 80% respectively in patients receiving cisplatin in that study[22] compared to 59.2% and 48.7% from our study. The other Italian study also reported better complete control of vomiting and nausea from more drug doses compared to our study. They found that 3 doses of 8 mg ondansetron and a single dose of 20 mg dexamethasone yielded complete control of vomiting and nausea for 74-77% and 66-80% in patients receiving cisplatin

of > 50 mg/m^2[23]. Hence, we conclude from our results that a single dose of 8 mg ondansetron in combination with 20 mg of dexamethasone is inadequate and should not be the standard prophylactic in cisplatin containing regimens of chemotherapy. We believe that higher dose of ondansetron may result in better control as those reported in the study of Hainsworth[15]. Further studies should add some other antiemetics in combination of ondansetron and dexamethasone or some agents should be used in stead of ondansetron for prophylaxis in cisplatin containing regimens of chemotherapy.

Another factor that influences the control of nausea and vomiting was patients' age. Rate of complete control of nausea and vomiting were higher in patients older than 45 years old. One could be doubtful that the higher control rate may bave been due to the tendency that older patients might have received carboplatin in stead of cisplatin. However, in multivariable analysis, age was the significant independent factor associated with control of both nausea and vomiting. In subgroup analysis of cisplatin and non-cisplatin containing regimens, age was still the significant or borderline significant factor in control of nausea and vomiting. This was in agreement with the study of the Italian Group for Antiemetic Research that younger patients of less than 50 years had a greater number of emetic episodes than older patients[23].

Concerning the persistent efficacy of the antiemetics in repeated courses of chemotherapy, this study showed that after the third course, the complete control of nausea was significantly decreased, while the complete control of vomiting was not significantly different. Another study[23] also showed that the efficacy in protection from vomiting and nausea by ondansetron in combination with dexamethasone slightly decreased during the second cycle.

Regarding the side effects of intravenous ondansetron, headaches were the most common event reported (18-25%)[24]. However, headache was complained in only 2.5% of the total chemotherapy cycle in this study. Other side effects of constipation and diarrhea were difficult to differentiate regarding the etiology, whether they were caused by ondansetron, chemotherapy itself, or combination of them.

In conclusion, this study has demonstrated that a single intravenous dose of 8 mg of ondansetron and 20 mg of dexamethasone had only few side effects, but had good control of nausea and vomiting only in the patients who received non-cisplatin containing regimens and those older than 45 years.

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การป้องกันอาการคลื่นไส้อาเจียนของ Ondansetron และ Dexamethasone ในผู้ป่วยมะเร็งนรีเวชที่ได้รับเคมีบำบัด

ปนัดดา ประเดิมดี, สุมนมาลย์ มนัสศิริวิทยา, ศิริวรรณ ตั้งจิตกมล, เถาวลัย ถาวรามร, พาชื่น ศึกวัฒนา

วัตถุประสงค์: *เพื่อศึกษาผลของ ondansetron และ dexamethasone ที่ให้เพียง 1 ครั้งในการป้องกันการเกิดอาการคลื่นไส้อาเจียนหลังได้รับเคมีบำบัดใน 24 ชั่วโมงแรก ตลอดจนศึกษาปัจจัยที่มีผลต่อการเกิดอาการคลื่นไส้อาเจียน*

วัสดุและวิธีการ: *ทำการศึกษาย้อนหลังในผู้ป่วยที่ได้รับ ondansetron 8 มิลลิกรัม และ dexamethasone 20 มิลลิกรัม เพียง 1 ครั้งเพื่อป้องกันการเกิดอาการคลื่นไส้อาเจียนหลังได้รับเคมีบำบัด ที่ภาควิชาสูติศาสตร์-นรีเวชวิทยา วิทยาลัยแพทยศาสตร์กรุงเทพมหานครและวชิรพยาบาล ตั้งแต่เดือนตุลาคม พ.ศ. 2547 ถึงเดือนเมษายน พ.ศ. 2549 และได้ประเมินประสิทธิภาพในการรักษาอาการคลื่นไส้อาเจียนในช่วง 24 ชั่วโมงแรกหลังได้รับเคมีบำบัด นำปัจจัยต่าง ๆ ได้แก่ อายุของผู้ป่วย ประวัติการดื่มสุรา ชนิดของมะเร็ง ชนิดของเคมีบำบัดและจำนวนครั้งของการได้รับเคมีบำบัดมาวิเคราะห์เพื่อหาปัจจัยเสี่ยงต่อการควบคุมอาการคลื่นไส้อาเจียน*

ผลการศึกษา: *ผู้ป่วยมะเร็งนรีเวช 78 ราย ได้รับเคมีบำบัดทั้งสิ้น 353 ครั้ง พบว่าสามารถควบคุมอาการคลื่นไส้และอาเจียนได้สมบูรณ์ 57.2% และ 68% ตามลำดับ โดยผู้ป่วยที่อายุ $\leq$ 45 ปี พบว่าสามารถควบคุมอาการคลื่นไส้และอาเจียนได้สมบูรณ์ 45.4% และ 56.9% ตามลำดับในขณะที่ผู้ป่วยที่อายุ > 45 ปี พบว่าสามารถควบคุมอาการคลื่นไส้และอาเจียนได้สมบูรณ์ 68.7% และ 78.8% ตามลำดับ ในผู้ป่วยที่ได้รับ cisplatin พบว่าสามารถควบคุมอาการคลื่นไส้และอาเจียนได้สมบูรณ์ 48.8% และ 59.2% ตามลำดับในขณะที่ผู้ป่วยที่ไม่ได้รับ cisplatin พบว่าสามารถควบคุมอาการคลื่นไส้และอาเจียนได้สมบูรณ์ 75.2% และ 86.7% ตามลำดับ เมื่อนำข้อมูลมาวิเคราะห์เชิงพหุพบว่าในกลุ่มผู้ป่วยที่อายุน้อยและได้รับ cisplatin จะสามารถควบคุมอาการคลื่นไส้และอาเจียนได้ต่ำกว่าอย่างมีนัยสำคัญทางสถิติ ในขณะที่ผู้ป่วยที่ได้รับเคมีบำบัดใน 3 ครั้งแรกจะสามารถควบคุมเฉพาะอาการคลื่นไส้ได้สมบูรณ์มากกว่าอย่างมีนัยสำคัญทางสถิติ*

สรุป: *การได้รับ ondansetron 8 มิลลิกรัม และ dexamethasone 20 มิลลิกรัมเพียง 1 ครั้ง สามารถควบคุมอาการคลื่นไส้อาเจียนได้ดีเฉพาะในกลุ่มที่ไม่ได้รับ cisplatin และในกลุ่มที่อายุ > 45 ปี*