Journal of Korean Medical Science
Vol. 9, No. 5, 369-375 October 1994

Ondansetron compared with Ondansetron plus Metoclopramide in the Prevention of Cisplatin-induced Emesis

Cheol-Whan Lee, M.D., Cheol-Won Suh, M.D., Jung-Shin Lee, M.D.,
Kyoo-Hyung Lee, M.D., Goo-Yeong Cho, M.D.,
Sang-We Kim, M.D., Sang-Hee Kim, M.D.

Department of Medicine, Asan Medical Center,
University of Ulsan, College of Medicine

To determine the contribution of metoclopramide to the efficacy of ondansetron in control of cisplatin-induced emesis, ondansetron was compared with ondansetron plus metoclopramide for antiemetic efficacy in a randomized double-blind trial. Enrolled 66 patients were treated with cisplatin(60mg/m²) in combination with etoposide, flourouracil, or vinblastine, and randomized to receive either ondansetron alone or ondansetron plus metoclopramide. Sixty patients were evaluable. Complete or major control of acute emesis was achieved in 96.6%(29/30) of patients given ondansetron plus metoclopramide and in 80%(24/30) receiving ondansetron alone, with no statistical significance(P=0.07). However, delayed emesis(days2-6) was better controlled by combination therapy than by ondansetron alone with 22 of 30(73.4%) and 11 of 30(36.7%), respectively(P=0.03). No major drug-related side effects were observed. These results suggest that ondansetron plus metoclopramide is superior to ondansetron alone in the control of cisplatin induced delayed emesis without significant side effects.

Key Words : *Ondansetron, Metoclopramide, Cisplatin, Emesis.*

INTRODUCTION

Cisplatin is known to be one of the the most emetogenic antineoplastic agents, but widely used in current combination chemotherapy for various kinds of cancer. Although ondansetron has provided effective control of acute emesis after cisplatin-containing chemotherapy, delayed emesis remains a distressing side effect of this drug(Kris et al., 1989 ; De Mulder et al., 1990 ; Marty et al., 1990 ; Roila et al., 1991a,b). Metoclopramide, a substitute benzamide, has a broad spectrum antiemetic activity for cisplatin and non-cispslatin chemotherapy regimens(Ogawa, 1982 ; Ogawa et al., 1982). Since ondansetron was introduced, the use of metoclopramide has been decreasing due to extrapyramidal symptoms. However, none of the widely used antiemetic drugs has controlled emesis satisfactorily. Despite its extrapyramidal effects metoclopramide is one of the most effective antiemetic agents with a wide range of therapeutic index, but there have been no studies to determine whether metoclopramide can enhance the efficacy of ondansetron in treating cisplatin-induced emesis.

Therefore, we conducted a prospective, rando-

Address for correspondence : *Cheol-Whan Lee, M.D., Department of Medicine, Asan Medical Center, Kang-Dong P.O. Box 145, Seoul, 134-600, Korea. Tel : (02)224-3330, Fax : (02)224-3260.*

mized, double-blind trial to compare ondansetron alone with ondansetron plus metoclopramide in the prophylaxis of acute and delayed emesis after cisplatin-based chemotherapy.

METHODS

Patients

Patients with histologically proven malignancy of 18 years or older who received cisplatin on the first treatment day of a combination chemotherapy regimen were entered into the trial. All patients had received no prior chemotherapy and had a performance status grade of more than 60 percent(Karnofsky scale). Patients were excluded from the study if they had vomited or retched 24 hours before the study, had received antiemetics during this period, had other etiologies for vomiting, were receiving concomitant radiation therapy, or had impaired renal function(serum creatinine>2mg/dl), jaundice (serum bilirubin>2.0mg/dl), or an elevated serum aminotransferase level(AST or ALT>twice the upper normal limit). Written informed consent was obtained from all participants.

Chemotherapy

Patients were hospitalized during treatment, and received cisplatin intravenously at a dose of 60mg/m^2 over 3 hours. Patients were hydrated with half saline at a rate of 120mL/h for 12 hours before and after cisplatin administration. All patients received treatment with cisplatin in combination with etoposide, flourouracil, or vinblastine

Antiemetic regimen

Patients were randomized in a double-blind fashion to receive either ondansetron plus metoclopramide or ondansetron plus placebo according to computer generated random code. All patients received ondansetron 0.15mg/kg intravenous injection 30 minutes before the start of cisplatin, and their second and third dose 4 and 8 hours after the initial dose, and took oral ondansetron(8mg three times a day) for five days(days 2-6). Metoclopramide or matched placebo(normal saline) was intravenously infused over 15 minutes at a does of 1mg/kg 30 minutes before the start of cisplatin and at a dose of 0.5mg/kg 4 hours and 8 hours after the initial dose. Thereafter, patients received oral metoclopramide(20mg four times a day) or matched placebo tablets for 5 days(days 2-6). No other antiemetics were used unless six or more episodes of emesis occurred.

Evaluation of Antiemetic Efficacy and Safety

Patients were observed daily during the 6-day period after initiation of cisplatin chemotherapy to detect the occurrence of emetic episodes or adverse events related to the study-drug. Data concerning nausea, emesis, and any adverse effects were recorded daily by the patients. Efficacy assessment of antiemetic treatment was based on the number of emetic episodes, the intensity of nausea, and the degree of food intake. An emetic episode was defined as a single episode of vomiting, a single episode of retching or any number of continuous vomiting or retching. Emetic episodes had to be separated from each other by the absence of vomiting or retching for at least 1 minute. The effect of therapy on emesis was graded as : complete response-no emetic episodes ; major response-one or two emetic episodes ; minor response-three to five emetic episodes ; or failure-more than 5 emetic episodes. Patients achieving complete or major response were regarded as a "success". The efficacy of therapy on nausea was graded as : none ; mild-did not interfere with normal daily life ; moderate-interfere with normal daily life ; or severe-confined to bed due to nausea. The degree of drowsiness and anxiety was also recorded on similar scales. Efficacy of therapy on food intake was graded as : 1-better than usual ; 2-as usual ; 3-could take some solid ; or 4-could take only liquid. Blood samples, to monitor complete blood cell counts and liver function, were obtained 24 hours before the first dose of the study drug and at day 7.

Statistical Analysis

Analyses were done separately for day 1(acute emesis), and days 2 through 6(delayed emesis). The analyses of days 2 through 6 were based on the "worst day" outcome. Treatment groups were compared with regard to all variables investigated during the 6-day study period using the Mann-Whitney U test. All tests were two tailed, and a p-value below 0.05 was considered statistically significant.

Table 1. Patients Characteristics*

Characteristic	OND (N=30)(%)	OND plus MXL (N=30)(%)
Age(yr)	54.2±15.3	52.5±13.4
Sex(Males/Females)	14/16	12/18
Performance		
0-1	28(93.3)	29(96.7)
2	2(6.7)	1(3.3)
Type of Cancer		
Stomach	18(60)	22(73.3)
Esophagus	3(10)	2(6.7)
Lung	8(26.7)	5(16.7)
MUO	1(3.3)	1(3.3)
Surgery		
Subtotal gastrectomy	10(33.3)	15(50)
Total gastrectomy	4(13.3)	4(13.3)
Pneumonectomy	2(6.7)	1(3.3)
None	14(46.7)	10(33.3)
Stage		
1	2(6.7)	0
2	4(13.3)	2(6.7)
3	17(56.7)	20(66.7)
4	7(23.3)	8(26.7)
Chemotherapy		
FP	22(73.3)	24(80)
MVP	7(23.4)	5(16.7)
EP	1(3.3)	1(3.3)
Alcohol use		
None	23(76.7)	24(80)
<7 drinks/week	4(13.3)	4(13.3)
previous heavy use	3(10)	2(6.7)

* There was no significant difference between the two groups.
Plus-minus values are means±SD.
MXL : metoclopramide.
MUO : malignancy of unknown origin.
OND : ondansetron.
EP : cisplatin(day 1) and etoposide(100mg/m^2, days 1-3).
FP : cisplatin(day 1) and flourouracil(1000mg/m^2, days 2-6).
MVP : cisplatin(day 1) and mitomycin(6mg/m^2, day 2) and vinblastin(6mg/m^2, day 2).

RESULTS

Between March 1993 and September 1993, a total of 66 patients from Asan Medical Center were enrolled in the study. Of these patients, 3 patients were excluded from the study because of receiving antiemetics within 24 hours before the study and 3 patients were not evaluable due to error in antiemetic administration(2 receiving ondansetron and 1 receiving ondansetron plus metoclopramide). Sixty patients(30 patients in each group) were fully evaluated for clinical efficacy. No patients were withdrawn from the study due to drug toxicity.

There were no differences between the two groups in age, sex, performance score, type of cancer, type of surgery, chemotherapy regimen, and alcohol consumption(Table 1).

Acute and delayed emesis

Details of the control of emesis regarding vomiting and retching on day 1 and "worst day" analysis of days 2-6 are shown in tables 2 and 3. On day 1, 80-96.6% of patients reported complete or major control of emesis with no difference between the two arms of the study(Table 2). However, delayed

Table 2. Acute Emesis

	OND (n=30)(%)	OND plus MXL (n=30)(%)	P value
Control of Emesis			
Complete response	23(76.7)	28(93.3)	0.07
Major response	1(3.3)	1(3.3)	
Partial response	6(20)	1(3.3)	
Failure	0	0	
Degree of Nauea			
None	13(43.3)	23(76.7)	0.02
Mild	8(26.7)	4(13.3)	
Moderate	7(23.3)	2(6.7)	
Severe	2(6.7)	1(3.3)	

MXL : metoclopramide, OND : ondansetron.

emesis(days 2-6) was better controlled by metoclopramide plus ondansetron than by ondansetron alone with 22 of 30(73.4%) and 11 of 30(36.7%), respectively(P=0.03).

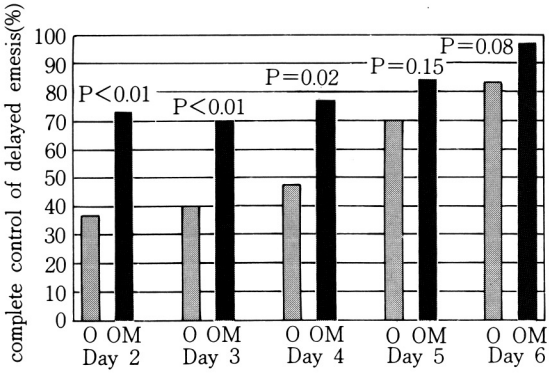

Fig. 1. Complete control of delayed emesis on days 2-6. O : ondansetron, OM : ondansetron plus metoclopramide.

Fig. 1 shows the proportions of complete protection from emesis during days 2 through 6. The addition of metoclopramide to the ondansetron regimen significantly reduced episodes of delayed emesis on days 2-4(days 2, 73.3% vs 36.7%, P< 0.01 ; days 3, 70.0% vs 40%, P<0.01 ; days 4, 76.7% vs 46.7%, P=0.02). However, there were no significant differences between the two groups on days 5-6(days 5, 83.3% vs 70%, P=0.15 ; days 6, 96.7% vs 83.3%, P=0.08).

Acute and delayed nausea

The severity of nausea is summarized in tables 3 and 4. The combination therapy was significantly superior to ondansetron alone in the control of nausea on day 1 and days 2 through 6. No nausea on day 1 was reported by 76.7% of patients with combination therapy and 43.3% of those taking ondansetron alone(P=0.02). Delayed nausea(days

Table 3. Delayed Emesis(Day 2-Day 6)

	OND (n=30)(%)	OND plus MXL (n=30)(%)	P value
Control of Emesis			
Complete response	6(20)	17(56.7)	0.03
Major response	5(16.7)	5(16.7)	
Partial response	5(16.7)	4(13.3)	
Failure	14(46.7)	4(13.3)	
Degree of Nauea			
None	2(6.7)	8(26.7)	0.04
Mild	3(10)	12(40)	
Moderate	14(46.7)	8(26.7)	
Severe	11(36.7)	2(6.7)	

MXL : metoclopramide, OND : ondansetron.

Table 4. Adverse reactions

Side Effects	OND (n=30)(%)	OND plus MXL (n=30)(%)	P value
Akathisia	0	3(10)	0.09
Constipation	3(10)	0	0.09
Headache	11(36.7)	6(20)	0.13
Hiccup	1(3.3)	1(3.3)	—
Sedation	1(3.3)	9(30)	0.03

MXL : metoclopramide, OND : ondansetron.

2-6) was also significantly better controlled by combination therapy than by ondansetron alone(26.7% vs 6.7%, P=0.04).

Food intake

Food intake was poor in both groups on days 1-6, but was generally better in patients with combination therapy than in those with ondansetron alone (Table 5).

Table 5. Food intake

Grade	OND(%)	OND plus MXL(%)	P value
1	0	0	<0.01
2	1(3.3)	3(10)	
3	11(36.7)	24(80)	
4	18(60)	3(10)	

MXL : metoclopramide, OND : ondansetron.

Safety

No major drug-related side effects were observed during treatment (Table 4). Patients receiving ondansetron alone reported more headaches and constipation, but the difference between groups was not statistically significant. Three patients receiving combination therapy reported transient akathisia on day 2, which was mild and resolved spontaneously. Drowsiness occurred in 7 patients given combination therapy(4 mild, 3 moderate), and the difference between groups was statistically significant(P=0.03). None of the changes in the biochemical or hematological parameters was attributed to antiemetic treatment.

DISCUSSION

This study demonstrates that metoclopramide can significantly enhance the antiemetic effect of ondansetron in the prophylaxis of cisplatin-induced emesis. Complete control of acute emesis was achieved in 93.3% of patients given combination therapy and in 76.7% of those receiving ondansetron alone, but the difference between treatments did not reach statistical significance(P=0.11). However, The combination therapy was significantly superior to ondansetron alone in the control of nausea during the acute phase(P=0.02). Our data for the complete control of acute emesis was similar to the previous reports which achieved complete control in about 90% with a combination of ondansetron and dexamethasone(Roila et al., 1991a,b ; Smyth et al., 1991). The statistical difference between nausea and emesis data during the acute phase may be explained by the fact that the number of study patients recruited in this study was small. Further studies will be necessary to demonstrate the enhancing effect of metoclopramide to ondansetron in treating acute emesis.

In our study, the addition of metoclopramide to ondansetron significantly reduced the incidence of delayed nausea and vomiting(P<0.01). Complete or major control of cisplatin-induced delayed emesis was achieved in 73.4% of patients treated with combination therapy compared with 36.7% of those given ondansetron alone. Although delayed emesis was not entirely prevented by ondansetron plus metoclopramide, these results are comparable to the previous results(Kris et al., 1987 ; Roila et al., 1991a,b). In contrast to superior effects in the treatment of acute emesis, ondansetron was reported to have similar effects to metoclopramide in the control of cisplatin-induced delayed emesis(Marty et al., 1990 ; Sledge et al., 1990). The causes of delayed nausea and emesis are not known. Even using the currently accepted standard dose of oral metoclopamide, ondansetron or dexamethasone(Kris et al., 1989 ; Marty et al., 1990 ; Sledge et al., 1990), con-

trol of delayed emesis was partially effective. In recent years, Gandara et al. performed a double-blind randomized trial comparing placebo with ondansetron for delayed emesis following cisplatin (>100mg/m^2). Rates of complete control of emesis were higher in ondansetron-treated patients during each day, but the differences were statistically superior only on the third study day(P=0.009)(Gandara et al., 1993). These results suggest that the delayed emesis may be partially mediated through the serotonin receptor. Therefore, serotonin may not be the sole mediator of the delayed emesis. However, delayed emesis may result from stimulation of the chemoreceptor trigger zone and/or vomiting center in the medulla oblongata, which contain various neurotransmitter receptors, such as dopamine receptor(D2), serotonin receptor, or histamine receptor(Peroutka et al., 1982). Therefore, drug combinations affecting more than one of these receptors may be more efficacious in the control of delayed emesis. Metoclopramide and ondansetron have been studied extensively in various combination antiemetic trials with some improvement of efficacy. Although there were a few reports of combinations of dopamine receptor blocker and serotonin receptor blocker(Bregni et al., 1991 ; Herrstedt et al., 1993), which led to improvement of antiemetic efficacy, the combination therapy of metoclopramide and ondansetron in the treatment of cisplastin-induced emesis was not reported. Metoclopramide, dopamine D2 antagonist, was a more potent and superior single-agent antiemetic drug when compared to other dopamine D2 receptor blockers(Gralla, 1981 ; Grunberg et al., 1984 ; Lindly et al., 1989). Metoclopramide is inexpensive and relatively safe except for extrapyramidal reactions, which can be easily controlled by appropriate therapy. In this study, a low dose of metoclopramide was used and, therefore, the antiemetic effect of metoclopamide was believed to be mediated by dopamine receptor D2(Fozard et al., 1978). The results of this trial confirm that in addition to serotonin receptor, dopamine receptor D2 plays an important role in treating cisplatin-induced delayed emesis and metoclopramide has the potential to enhance the effect of ondansetron.

Mild or moderate headache, constipation, sedation, and akathisia were the most commonly reported adverse events with both treatments. However, all the observed side effects were mild and self-limited, and all patients were well tolerated.

In conclusion, the addition of metoclopramide clearly improved the antiemetic efficacy of ondansetron for the control of cisplatin-induced delayed emesis without significant side effects. However, further combinations of antiemetics with different mechanisms of action will be necessary for more complete control of cisplatin-induced delayed emesis.

REFERENCES

Bregni M, Siena S, Di Nicola M, Bonadonna G, Gianni AM . *Tropisetron plus haloperidol to ameliorate nausea and vomiting associated with high-dose alkylating agent cancer chemotherapy. Eur J Cancer 1991 ; 27 : 561-5.*

De Mulder PHM, Seynaeve C, Vermorken JB, van Liessum PA, Mols-Jevdevic S, Allman EL, Beranek P, Verweij J . *Ondansetron compared with high-dose metoclopramide in prophylaxis of acute and delayed cisplatin-induced nausea and vomiting ; A multicenter, randomized double-blind, crossover study. Ann Intern Med 1990 ; 113 : 834-40.*

Fozard JR, Mobarok Ali ABU TM . *Blockade of neuronal tryptamine receptors by metoclopramide. Eur J Pharm 1978 ; 49 : 109-12.*

Gandara DR, Harvey WH, Monaghan GG, Perez EA, Hesketh PJ . *Delayed emesis following high-dose cisplatin comparative trial of ondansetron versus placebo. Eur J Cancer 29A, Suppl 1993 ; 1 : S35-8.*

Gralla RJ, Itri IM, Pisko SE, Squillante AE, Kelsen DP, Braun DW, Bordin LA, Braun TJ, Young CW . *Antiemetic efficacy of high dose metoclopramide ; Randomized trials with placebo and prochlorperazine in patients with chemotherapy-induced nausea and vomiting. N Engl J Med 1981 ; 305 : 905-9.*

Grunberg SM, Gala KV, Lampenfeld M, Jamin D, Johnson K, Cariffe P, Strych D, Krailo M . *Comparison of the antiemetic effect of high-dose intravenous metoclopramide and high dose intravenous haloperidol in a randomized double blind crossover study. J Clin Oncol 1984 ; 2 : 782-7.*

Herrstedt J, Sigsgaard T, Boesgaard M, Jensen TP, Dombernowsky P . *Ondansetron plus metopimazine compared with ondansetron alone in patients receiving moderately emetogenic chemotherapy. N Engl J Med 1993 ; 328 : 1076-80.*

Kris MG, Gralla RJ, Clark RA, Tyson LB, Groschen S . *Antiemetic control and prevention of side effects of anticancer chemotherapy with lorazepam or diphenhydramine when used in combination with metoclopramide plus dexamethason. Cancer 1987 ; 60 : 2816-22.*

Kris MG, Gralla J, Tyson LB, Clark RA, Cirrincione C, Groshen S . *Controlling Delayed Vomiting ; Double-Blind, Randomized Trial Comparing Placebo, De-*

xamethason Alone, and Metoclopramide plus Dexamethason in Patients Receiving Cisplatin. J Clin Oncol 1989 ; 7 : 108-14.

Lindly CM, Bernard S, Fields SM . *Incidence and Duration of Chemotherapy-Induced Nausea and Vomiting in the Outpatient Oncology Population. J Clin Oncol 1989 ; 7 : 1142-9.*

Marty M, Pouillart P, Scholl S, Droz JP, Azab M, Brion N, Pujade-Lauraine E, Paule B, Paes D, Bons J . *Comparison of the 5-hydroxytryptamine$_3$(serotonin) antagonist ondansetron(GR 38032F) with high-dose metoclopramide in the control of cisplatin-induced emesis. N Engl J Med 1990 ; 322 : 816-21.*

Ogawa GS . *Metoclopramide as an antiemetic in chemotherapy. N Engl J Med 1982 ; 307 : 249-50.*

Ogawa GS, McDermed JE, Opfell RW, Riech LP . *Intravenous metoclopramide ; an effective antiemetic in cancer chemotherapy. JAMA 1982 ; 247 : 2683-6.*

Peroutka SJ, Snyder SH . *Antiemetics ; neurotransmitter receptor binding predicts therapeutic actions. Lancet 1982 ; 1 : 658-9.*

Roila F, Newlands ES, Rustin GJS, Begent RHJ, Howells N, Macquade B, Bagshawe KD . *Comparison of ondansetron and ondansetron plus dexamethasone as antiemetic prophylaxis during cisplatin-containg chemotherapy. Lancet 1991 ; 338 : 487-90(a).*

Roila F, Tonato M, Cognetti F, Cortesi E, Favalli G, Marangolo M, Amadori D, Bella MA, Gramazio V, Donati D, Ballatori E, Favero AD . *Prevention of Cisplatin-Induced Emesis ; A Double-Blind Multicenter Randomized Crossover Study Comparing Ondansetron and Ondansetron Plus Dexmethasone. J Clin Oncol 1991 ; 9 : 675-8(b).*

Sledge GW, Einhorn LH, Nagy C, Finn AL, Patrick SE . *Randomised trial of ondansetron(OND) and metoclopramide(MCP) as antiemetic therapy for cisplatin-based chemotherapy. Proc Am Soc Clin Oncol 1990 ; 9(abstract) : 323.*

Smyth JF, Coleman RE, Nicolson M, Gallmeier WM, Leonard RCF, Cornbleet MA, Allan SG, Upadhyaya BK, Bruntsch U . *Does dexamethasone enhance control of acute cisplatin induced emesis by ondansetron Br Med J 1991 ; 303 : 1423-6.*