Comparison of Intermittent Ondansetron Versus Continuous Infusion Metoclopramide Used with Standard Combination Antiemetics in Control of Acute Nausea Induced by Cisplatin Chemotherapy

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Background. **Ondansetron is a serotonin antagonist that recently has been introduced as a preventive agent for chemotherapy-induced nausea and vomiting. The current study was performed to determine the degree of antiemetic control of ondansetron in combination with dexamethasone and lorazepam, and to compare this combination to the previously very effective regimen of lorazepam, dexamethasone, diphenhydramine, and continuous-infusion metoclopramide.**

Methods. **Eighty chemotherapy-naive patients with newly diagnosed neoplasms undergoing cisplatin combination chemotherapy were randomized to receive one of two combination antiemetic regimens: lorazepam, dexamethasone, intermittent intravenous ondansetron; or lorazepam, dexamethasone, continuous-infusion metoclopramide, and diphenhydramine.**

Results. **There was major control (0–1 episodes) of acute nausea–vomiting in all of the patients receiving the ondansetron combination antiemetic regimen, which was significantly better ($P < 0.05$) than the major control of the acute nausea–vomiting of the patients receiving the metoclopramide combination antiemetic regimen. The ondansetron-treated patients experienced only a mild headache as their only toxicity and had significantly (P 0.0026) less diarrhea, akathisia, and acute dystonic reactions than the patients receiving the metoclopramide regimen. Delayed nausea was controlled with prophylactic prochlorperazine.**

Conclusions. **The ondansetron regimen was more effective and less toxic, but its cost was 20 times more than the metoclopramide regimen. *Cancer* 1993; 72:583–6.**

Key words: ondansetron, metoclopramide, antiemetic, chemotherapy, cisplatin.

Ondansetron is a serotonin antagonist that recently has been introduced as a preventive agent for chemotherapy-induced nausea and vomiting.[1–4] A number of studies have shown that ondansetron has antiemetic activity in patients receiving cisplatin chemotherapy[2,3] as well as noncisplatin combination chemotherapy such as alkylating agents and anthracyclines.[5–7] As a single agent, ondansetron has been shown to be more effective than placebo[8] and more effective than the antiemetic metoclopramide in patients receiving cisplatin.[9–11] In addition, the antiemetic effect of ondansetron appears to be enhanced by the addition of dexamethasone in controlling the acute nausea induced by cisplatin chemotherapy.[12–14] One study has compared ondansetron plus dexamethasone with a combination of metoclopramide, dexamethasone, and diphenhydramine, and suggested a superiority of the ondansetron regimen.[15]

We showed that the use of continuous-infusion metoclopramide in combination with intravenous dexamethasone, diphenhydramine, and lorazepam was a very effective combination antiemetic regimen to prevent acute nausea in patients receiving cisplatin chemotherapy.[16] Total control of acute nausea and vomiting was achieved in 90% of patients receiving moderately high-dose cisplatin chemotherapy with few toxicities. The continuous-infusion metoclopramide combination

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Table 1. Patient Profile

	Ondansetron combination	Metoclopramide combination
No. of newly diagnosed cancer patients	40	40
Age (yr)		
Median	63	65
Range	36–71	38–73
Gender		
Male	27	27
Female	13	13
History of alcoholism	3	4
Karnofsky index (≥ 80)	40	40
Pathology/chemotherapy		
Lung cancer		
Small cell (cisplatin/etoposide)	8	7
Non-small cell (cisplatin/etoposide)	15	15
Ovarian (cisplatin/cyclophosphamide)	4	4
GI tract (cisplatin/5-FU)	6	6
Head/neck (cisplatin/5-FU)	4	4
Bladder (cisplatin/methotrexate/vinblastine)	3	4
Cisplatin dose		
70 mg/m^2	3	3
80 mg/m^2	35	35
100 mg/m^2	2	2

GI: gastrointestinal; 5-FU: 5-fluorouracil.

antiemetic regimen was more effective in total control of acute nausea and vomiting and had less toxicity than previously used intermittent-bolus metoclopramide regimens.[16]

Ondansetron used alone appears to be a more effective antiemetic than metoclopramide used alone in patients receiving cisplatin, but the total control of acute nausea is only approximately 40% to 65% in the published studies.[9–11] The current study was performed to determine the degree of antiemetic control of ondansetron in combination with dexamethasone and lorazepam, and to compare this combination to the previously very effective regimen of lorazepam, dexamethasone, diphenhydramine, and continuous-infusion metoclopramide.

Patients and Methods

Eighty patients with newly diagnosed malignant neoplasms who were chemotherapy-naive received chemotherapy in the form of cisplatin (70–100 mg/m^2, intravenously, over 3 hours on day 1) and other chemotherapy agents, primarily etoposide for lung neoplasms, 5-fluorouracil for gastrointestinal tract or head and neck neoplasms, cyclophosphamide for ovarian neoplasms, or methotrexate and vinblastine for bladder neoplasms (Table 1). After informed consent was obtained, patients were randomized to receive antiemetics in the form of dexamethasone, lorazepam, and either intermittent intravenous ondansetron or intravenous metoclopramide, a loading dose followed by a continuous infusion, along with diphenhydramine. The doses of the individual antiemetic regimens are outlined in Table 2. Eighty patients were randomized, with 40 patients in each group; Table 1 shows that the two groups were balanced for gender, age, alcohol history, chemotherapy regimen, and cisplatin dose. This was a single-blinded study.

The antiemetic regimen was begun 30 to 60 minutes before the initiation of systemic chemotherapy. Patients were then observed for the following 24 hours for the number of episodes of vomiting, acute dystonic reactions, diarrhea, akathisia, or restlessness. Each patient was interviewed after the 24-hour period for subjective

Table 2. Antiemetic Regimens

Lorazepam	1 mg IV
Dexamethasone	10 mg IV every 4 hr for 3 doses
Ondansetron	0.15 mg/kg IV every 4 hr for 3 doses
	or
Lorazepam	1 mg IV
Dexamethasone	10 mg IV every 4 hr for 3 doses
Metoclopramide	1 mg/kg IV bolus; 0.5 mg/kg/hr for 10 hr
Diphenhydramine	0.5 mg/kg IV every 4 hr for 3 doses

Table 3. Results

Regimen	Evaluable patients	No. of episodes of acute nausea/vomiting			Induced toxicities				
		0	*1*	*> 1*	*Diarrhea*	*Acute dystonic reactions*	*Akathisia*		Headaches
Ondansetron combination	40	37	3	0	0	0	0	0.0026	6
Metoclopramide combination	40	36	0	4	3	3	3		3
				0.05					0.29

episodes of nausea, restlessness, excess sedation, or any unexpected toxicities. Nausea was defined as feeling as if one would vomit, and vomiting episodes were defined as beginning with gagging, throwing up fluid, and ending when all gagging and throwing-up terminated for at least 5 minutes. Diarrhea was defined as watery stools. The chemotherapy regimens lasted 3 to 5 hours, with the cisplatin given as the initial agent as a 3-hour infusion, etoposide given as a 2-hour infusion, cyclophosphamide given as a 1-hour infusion, and other chemotherapy agents given as bolus injections. 5-Fluorouracil was given as a prolonged infusion (72–96 hours) in the eight patients with head and neck neoplasms.

After the observation period of 24 hours, patients who had zero to one episode of acute nausea–vomiting were given oral prochlorperazine spansules (30-mg sustained-released capsules) every 12 hours for the next 72 hours to prevent delayed nausea–vomiting. Patients who experienced more than one episode of acute nausea and vomiting within a 24-hour observation period subsequently were administered intravenous bolus prochlorperazine (10 mg) every 3 hours as needed until the acute nausea–vomiting was controlled for 24 hours. They were then given the oral 30-mg prochlorperazine spansules every 12 hours for 72 hours.

To evaluate whether one antiemetic regimen was more effective than the other, as well as whether there were differences in toxicities between the two antiemetic regimens, the data were subjected to the Fisher exact test for the significance of changes, as well as the chi-square test.[17]

Results

Table 3 outlines the results of the effectiveness of the antiemetic regimens. Eighty patients were involved in the study, with 40 patients receiving the ondansetron combination antiemetic regimen and 40 patients receiving the continuous-infusion metoclopramide antiemetic regimen.

Thirty-seven of the 40 patients who received the ondansetron combination had complete control of nausea–vomiting, and all 40 patients had major control (0–1 episodes of nausea–vomiting). Thirty-six of the 40 patients who received the continuous-infusion metoclopramide regimen had complete control of nausea–vomiting, and 4 patients had poor control (> 1 episode of nausea–vomiting). Every patient who had an episode of vomiting had associated nausea. No patient had nausea with no vomiting.

The only toxicity noted in the patients receiving the ondansetron regimen was headache in 6 of 40 patients. The headache in all six patients was controlled with a nonnarcotic analgesic and lasted less than 4 to 6 hours in each case.

Patients receiving the metoclopramide regimen did experience some episodes of diarrhea, akathisia, and acute dystonic reactions. Of the nine induced toxicities observed, eight occurred in different individuals, with only one person experiencing two side effects.

In the postchemotherapy interview, patients did not report any excessive sedation or unexpected toxicities from either antiemetic regimen.

Of the 40 patients who received the ondansetron, 4 experienced more than one episode of delayed nausea and vomiting during the 72-hour period of prochlorperazine spansule administration. Of the 40 patients who received the metoclopramide combination, 5 experienced more than one episode of delayed nausea and vomiting. Three of the five patients were those who had poor control of acute nausea–vomiting. There was no difference ($P = 0.6$) between the number of episodes of delayed nausea and vomiting in the two groups, and there were no reported or observed toxicities from the prochlorperazine spansules.

Of the four patients who had poor control of acute nausea–vomiting with the metoclopramide regimen, all required at least three additional doses of intravenous prochlorperazine to control the acute nausea–vomiting.

Discussion

The results of this study show that when ondansetron is used in combination with dexamethasone and lorazepam, there is total or major control of the acute nausea/vomiting in all patients receiving cisplatin chemother-

apy, with only mild headache as the major toxicity. In addition, the ondansetron combination antiemetic regimen was significantly better ($P < 0.05$) in controlling acute nausea–vomiting than the metoclopramide combination antiemetic regimen, even though this latter regimen gave 90% complete control, as reported in our previous study.[16] The ondansetron regimen was effective without any induced diarrhea, akathisia, or acute dystonic reactions, significantly different ($P < 0.0026$) than the metoclopramide regimen.

Delayed nausea–vomiting was well controlled in patients receiving either antiemetic regimen using the prochlorperazine spansules. Excellent control of acute nausea–vomiting appears to translate into a lower incidence of delayed nausea when prophylaxis for delayed nausea is used.[15,16,18] Delayed nausea and vomiting is less frequent and is easier to control in patients who receive cisplatin in doses less than 100 mg/m^2.

A major difference between the two antiemetic regimens is cost, with the ondansetron antiemetic regimen ($310.72) being 20 times more expensive than the metoclopramide regimen ($15.78). This is due primarily to the cost of ondansetron, which may be reduced when additional serotonin antagonist antiemetics are available for general use.

References

1. Hesketh PJ, Gandara DR. Serotonin antagonists: a new class of antiemetic agents. *J Natl Cancer Inst* 1991; 83:613–20.
2. Einhorn LH, Nagy C, Werner K, Finn AL. Ondansetron: a new antiemetic for patients receiving cisplatin chemotherapy. *J Clin Oncol* 1990; 8:731–5.
3. Khojasteh A, Sartiano G, Tapazoglou E, Lester E, Gandara D, Bernard S, et al. Ondansetron for the prevention of emesis induced by high-dose cisplatin. *Cancer* 1990; 66:1101–5.
4. Grunberg SM. Will it play in Peoria? *J Clin Oncol* 1991; 9:713–5.
5. Bonneterre J, Chevallier B, Metz R, Fargeot P, Pujade-Lauraine E, Spielmann M, et al. A randomized double-blind comparison of ondansetron and metoclopramide in the prophylaxis of emesis induced by cyclophosphamide, fluorouracil, and doxorubicin or epirubicin chemotherapy. *J Clin Oncol* 1990; 8:1063–9.
6. Cubeddu LX, Hoffman IS, Fuenmayor NT, Finn AL. Antagonism of serotonin S3 receptors with ondansetron prevents nausea and emesis induced by cyclophosphamide-containing chemotherapy regimens. *J Clin Oncol* 1990; 8:1721–7.
7. Fraschini G, Ciociola A, Esparza L, Templeton D, Holmes FA, Walters RS, et al. Evaluation of three oral dosages of ondansetron in the prevention of nausea and emesis associated with cyclophosphamide-doxorubicin chemotherapy. *J Clin Oncol* 1991; 9:1268–74.
8. Cubeddu LX, Hoffman IS, Fuenmayor NT, Finn AL. Efficacy of ondansetron and the role of serotonin in cisplatin induced nausea and vomiting. *N Engl J Med* 1990; 322:810–6.
9. DeMulder PHM, Seynaeve C, Vermorken JD, Van Liessum PA, Mols-Jevdevic S, Allman EL, et al. Ondansetron compared with high-dose metoclopramide in prophylaxis of acute and delayed cisplatin-induced nausea and vomiting. *Ann Intern Med* 1990; 113:834–40.
10. Hainsworth J, Harvey W, Pendergrass K, Kasimis B, Oblon D, Monaghan G, et al. A single blind comparison of intravenous ondansetron, a selective serotonin antagonist with intravenous metoclopramide in the prevention of nausea and vomiting associated with high-dose cisplatin chemotherapy. *J Clin Oncol* 1991; 9:721–8.
11. Marty M, Pouillart P, Scholl S, Droz JP, Azab M, Brion N, et al. Comparison of the 5-hydroxytryptamine-serotonin antagonist ondansetron with high-dose metoclopramide in the control of cisplatin-induced emesis. *N Engl J Med* 1990; 322:816–21.
12. Roila F, Tonato M, Cognetti F, Cortesi E, Favalli G, Marangolo M, et al. Prevention of cisplatin induced emesis: a double blind multicenter randomized crossover study comparing ondansetron and ondansetron plus dexamethasone. *J Clin Oncol* 1991; 9:675–8.
13. Smith DB, Newlands ES, Rustin GJS, Begent RHJ, Howells N, McQuade B, et al. Comparison of ondansetron and ondansetron plus dexamethasone as antiemetic prophylaxis during cisplatin-containing chemotherapy. *Lancet* 1991; 1:487–90.
14. Smyth JF, Coleman RE, Nicholson M, Gallmeier WM, Leonard RCF, Cornbleet MA, et al. Does dexamethasone enhance control of acute cisplatin induced emesis by ondansetron? *Br Med J* 1991; 303:1423–6.
15. Italian Group for Antiemetic Research. Ondansetron + dexamethasone vs. metoclopramide + dexamethasone + diphenhydramine in prevention of cisplatin-induced emesis. *Lancet* 1992; 1:96–9.
16. Navari RM. Comparison of intermittent versus continuous infusion metoclopramide in control of acute nausea induced by cisplatin chemotherapy. *J Clin Oncol* 1989; 7:943–6.
17. Sokal RR, Rohlf FJ. Biometry. New York: Freeman, 1981.
18. Roila F. Predictive factors of delayed emesis in cisplatin-treated patients and antiemetic activity and tolerability of metoclopramide or dexamethasone: a randomized single-blind study. *Am J Clin Oncol* 1991; 14:238–42.