原　著

Comparison of Antiemetic Effects of Ondansetron and High-Dose Metoclopramide in Cisplatin-Based Chemotherapy

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ABSTRACT

Background. Cisplatin-induced nausea and emesis, mediated through the 5-hydroxytryptamine (serotonin) 5-HT_3 receptors, remains one of the most distressing side effects of chemotherapy for patients with cancer. Ondansetron, a 5-HT_3 receptor antagonist, has been developed for prevention of chemotherapy-induced nausea and emesis. Its antiemetic efficacy and adverse effects have rarely been studied in the aged Chinese cancer patients. We compared ondansetron with high-dose metoclopramide, a traditional standard antiemetic, in twenty-six chemotherapy-naive patients aged beyond 55, who were treated with cisplatin-based regimens for urogenital malignancy.

Methods. Patients received either ondansetron (n=13) or high-dose metoclopramide (n=13) as their only antiemetic during cisplatin treatment on voluntary choice. Antiemetic was given intravenously on day 1 (acute phase) and orally from day 2 to day 6 (delayed phase). Nausea and emesis were assessed and recorded according to a graded scale.

Results. In acute phase, ondansetron was superior to metoclopramide in control of both nausea (P = 0.008) and emesis (P = 0.013) by Wilcoxon rank sum test. Ondansetron was also better in regard of eliminating nausea (P = 0.007) and complete control of emesis (P = 0.003) by Fisher's exact test. In delayed phase, however, day-by-day comparison by Wilcoxon rank sum test revealed equal antiemetic efficacy on day 2 and day 3 , whereas metoclopramide was better from day 4 to day 6. Diarrhea occurred more frequently with metoclopramide (46.2%) than with ondansetron (0%). Extrapyramidal symptom appeared in one patient (7.7%) taking metoclopramide and none (0%) taking ondansetron.

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Conclusion. Ondansetron is effective and safe when injected intravenously for prevention of nausea and emesis induced by cisplatin-based chemotherapy chiefly in the acute phase. During delayed phase, however, it is not superior to metoclopramide.

Key Words: Ondansetron, Metoclopramide, Eemsis, Cisplatin.

Introduction

Despite the remarkable progress of cancer chemotherapy in the past several decades, emesis remains one of the most distressing side effects of cytotoxic treatment. Study of neuropharmacology has demonstrated that emesis induced by anticancer therapy is mediated through emetic reflex involving 5-hydroxytryptamine (serotonin) 5-HT_3 receptors contained in the area postrema and the abdomen visceral afferent nerves[1]. High-dose metoclopramide has been demonstrated as an effective regimen in control of cisplatin-induced emesis[2], and since then, it has been the cornerstone of effective antiemetic combinations[3]. However, it can induce intolerable extrapyramidal reactions especially in the youth[4], because metoclopramide acts as antagonist for both 5-HT_3 and dopamine receptors[5]. Ondansetron, a specific antagonist for 5-HT_3 receptors, has recently been developed and proven to be very effective in control of cisplatin-induced nausea and emesis[6]. In this study, either ondansetron or high-dose metoclopramide was prescribed as the single antiemetic therapy for patients aged beyond 55 who received cisplatin-containing regimens as their first systemic treatment for urogenital malignancy. The goal was to see whether they made significant difference in antiemetic efficacy and side effects in aged chemotherapy-naive patients.

Material and Methods

Patients

Thirty patients with urogenital cancer were enrolled in this study and divided into two groups to receive antiemetic therapy. They received based on voluntary choice after thorough explanation of the object and procedure of the study. Originally, there were 17 in the ondansetron group and 13 in the metoclopramide group. Four patients were finally excluded from the ondansetron group, including one with gastrointestinal obstruction as the major cause of vomiting, one with conditioned emesis that took place prior to infusion of chemotherapeutic drugs, and the other two who did not cooperate in evaluation of emesis after ondansetron injection and withdrew. The characteristics of the remaining evaluable 26 patients are listed in Table 1. All of them had malignancy of the urogenital organs and did not receive systemic chemotherapy before this study. Cisplatin-based chemotherapy was prescribed either for treatment of metastatic disease or as a postoperation adjuvant. Three different chemotherapy protocols were prescribed, CMV, MVAC and PF (Table 2) and cisplatin was given as a single dose infusion in

all of them, with the dosage adjusted accroding to creatinine clearance rate (Ccr) . When Ccr was below 60 ml/min, cisplatin was reduced to half of its scheduled dosage. As we can see in Table 1, most of the patients received CMV as their chemotherapy regimen and the cisplatin dose actually infused was balanced between both groups of patients.

Cisplatin and Antiemetic Therapy

Hydration with 2 litters of normal saline and 1 litter of 5% dextrose began 18 to 24 hours before cisplatin infusion for all patients. Additional 1 litter of normal saline was infused for two hours prior to a 30-minute infusion of 250 ml 20% mannitol, followed immediately by infusion of cisplatin contained in 500 ml normal saline for two hours. At the end of cisplatin infusion, 40 mg of furosemide was given through rapid intravenous dripping (IVD).

Table 1. Patient Characteristics

		Ondansetron	Metoclopramide
Age	Range (Mean)	57 - 73 (65)	59 - 80 (67)
Sex	Male/Female	12 /1	12 /1
Transitional	Bladder	8	7
Cell Ca.	Kidney	2	2
	Urethra	1	
Epidermoid Ca.	Bladder	1	
	Penis	1	1
	Anus		1
Paget's Disease	Scrotum		1
	Penis		1
Chemotherapy	CMV	12	11
	MVAC	1	
	PF		2
Cisplatin Dose	> 70 mg/sqm	9	9
	< 70 mg/sqm	4	4

Table 2. Chemotherapy Protocols

Protocol		Dose (mg/sqm)	Schedule
CMV	Cisplatin	100	Day 2
	Methotrexate	30	Day 1, 8
	Vinblastine	4	Day 1, 8
MVAC	Methotrexate	30	Day 1 15, 2
	Vinblastine	3	Day 2, 15, 2
	Adriamycin	30	Day 2
	Cisplatin	70	Day 2
PF	Cisplatin	75	Day 1
	Fluorouracil	1000	Day 1 to 5

Antiemetic therapy began 30 minutes before cisplatin infusion. For patients in the ondansetron group, 8 mg ondansetron IVD for 15 minutes was prescribed as the loading dose, followed by continuous infusion of ondansetron, 1 mg/hr, contained in 5% dextrose, for 24 hours. Immediately after that, ondansetron was taken orally, 8 mg every 8 hours for 15 doses.

For patients in the high-dose metoclopramide group, a loading dose of metoclopramide, 3 mg/kg, was infused for 30 minutes. After that, a 24-hour continuous infusion of metoclopramide, 0.5 mg/kg/hr, began along with cisplatin infusion. Oral metoclopramide, four times a day, 10 mg every time, totally 20 doses, was taken immediately after intravenous metoclopramdie infusion.

The patients received either ondansetron or high-dose metoclopramide as their only antiemetic therapy during this study. No other antiemetics, including diphenhydramine, prochlorperazine, chlorpromazine, dexamethasone, and benzodiazepine, such as lorazepam, was permitted within 24 hours before cisplatin infusion or throughout the study, except for rescue medication in condition of treatment failure, defined as over 5 emetic episodes within the first 24 hours after cisplatin infusion.

Evaluation of Emesis Control

Control of nausea and emesis was assessed and recorded using a graded scale indicating how nausea interfered with daily life and the number of emetic episodes every 24 hours as shown in Table 3. Any vomit productive of liquid or dry retch in a 5-minute period was scored as a single emetic episode. A diary card was kept by the patient to record the scales of emesis and any other discomfort during the study. The whole course was divided into two phases. The acute phase referred to the first 24 hours (day 1) after cisplatin infusion and the delayed phase lasted from day 2 to day 6.

Statistics

Total absence of nausea and complete control of emesis between ondansetron and high-dose metoclopramide in the acute

Table 3. Evaluation of Nausea and Emesis

Nausea grade		
	None	Nausea totally absent
	Mild	Not interfering with normal daily life
	Moderate	Interfering with normal daily life
	Severe	Bedridden due to nausea
Emesis control		Episodes/Day
	Complete	0
	Major	1 - 2
	Minor	3 - 5
	Failure	> 5 or rescued

phase were compared by Fisher's exact test. A thorough evaluation of the antiemetic effects of ondansetron and high-dose metoclopramide was conducted by Wilcoxon rank sum test (normal approximation method one-sided level alpha test) for both the acute and delayed phases. In the delayed phase, the test was performed on a day-by-day basis.

Results

Control of nausea is listed in Table 4. In the acute phase (day 1), nausea was found to disappear in 6 patients of the ondansetron group (6/13, 46.2%) but in none

Table 4. Control of Nausea

		None	Mild	Moderate	Severe
Ondansetron					
	Day 1	6	4	3	0
	Day 2	6	3	4	0
	Day 3	5	3	1	4
	Day 4	6	2	3	2
	Day 5	7	4	0	2
	Day 6	10	3	0	0
Metoclopramide					
	Day 1	0	6	3	4
	Day 2	2	6	5	0
	Day 3	7	6	0	0
	Day 4	12	1	0	0
	Day 5	13	0	0	0
	Day 6	13	0	0	0

Table 5. Control of Emesis

		Complete	Major	Minor	Failure
Ondansetron					
	Day 1	7	2	1	3
	Day 2	6	1	2	4
	Day 3	6	3	4	0
	Day 4	6	6	1	0
	Day 5	7	5	1	0
	Day 6	10	3	0	0
Metoclopramide					
	Day 1	0	7	0	6
	Day 2	2	5	6	0
	Day 3	7	4	2	0
	Day 4	12	1	0	0
	Day 5	13	0	0	0
	Day 6	13	0	0	0

of the metoclopramide group (0/13, 0%). The difference was significant by Fisher's exact test (P = 0.007).

Control of emesis is listed in Table 5. In the acute phase (day 1), the rate of complete control of emesis was 53.8% in the ondansetron group (7/13) and 0% in the metoclopramide group (0/13), which was significantly different by Fisher's exact test (P = 0.003).

The control of nausea and emesis in the acute phase between ondansetron and metoclopramide was compared by Wilcoxon rank sum test (normal approximation method one-sided level alpha test) to show statistically better antiemetic effects of ondansetron for cisplatin-based chemotherapy (P = 0.008 and 0.013 for nausea and emesis, respectively.).

However, when Wilcoxon rank sum test was conducted for day-by-day comparison in the delayed phase , the result was different (Table 4&5). Ondansetron and metoclopramide seemed to make no difference in control of nausea and emesis on day 2 and day 3. From day 4 to day 6, however, metoclopramide seemed to have better control of both nausea and emesis (P = 0.116, 0.064, 0.005, 0.004 and 0.04, respectively, for nausea control and 0.447, 0.270, 0.007, 0.004 and 0.04, respectively, for emesis control).

The numbers of patient with complaints other than nausea and emesis throughout the study course are listed in Table 6. Weakness, fatigue, dizzness, cough, fever and hiccup were more related to the underlying diseases or chemotherapy rather than the antiemetics, and were grouped together. The other group of symptoms including diarrhea, abdomen discomfort, constipation, headache and extrapyramidal symptoms were probably side effects of antiemetics. Diarrhea was complained in 46.2% (6/13) of patients in the metoclopramide group but none in the ondansetron group. The difference was significant, (P = 0.007 by Fisher's exact test). Constipation and headache occurred in 7.7% (1/13) of patients for ondansetron and none for metoclopramide. Restlessness, an apparent extrapyramidal symptom (EPS), appeared in one patient during high-dose metoclopramide infusion and was the only episode of EPS observed.

Table 6. Symptoms during Antiemetic Treatment

	Ondansetron	Metoclopramide
I.		
Weakness/Fatigue	4 (30.8%)	5 (38.5%)
Dizzness	2 (15.4%)	7 (53.8%)
Cough	1 (7.7%)	0
Fever	1 (7.7%)	0
Hiccup	1 (7.7%)	0
II.		
Diarrhea	0	6 (46.2%)
Abdomen Discomfort	0	1 (7.7%)
Constipation	1 (7.7%)	0
Headache	1 (7.7%)	0
Extrapyramidal sign	0	1 (7.7%)

Discussion

Although this study was not a randomized trial, the distribution of evaluable patients between both treatment groups in regard of age, sex, diagnosis, chemotherapy protocol and cisplatin dose received was satisfactorily balanced as shown in Table 1. Most of the patients received the same chemotherapy regimen containing cisplatin, methotrexate and vinblastine. To our knowledge and experience, neither methotrexate nor vinblastine in this protocol showed emetic problems in spite that they were injected 24 hours before cisplatin, which, therefore is the main concern in this emesis control study.

It has been established that no advantage accrues to the use of metoclopramide in excess of 3 mg/kg for control of emesis induced by chemotherapy including cisplatin[7]. Even with this traditionally adequate loading dose of metoclopramide followed by a maintenance therapy through continuous infusion for 24 hours, the antiemetic effects of metoclopramide is found to be inferior to that of ondansetron, a 5-HT_3 receptor antagonist, in the acute phase. The result is compatible with a previous comparative study adopting nearly the same ondansetron and metoclopramide protocol with ours, but the maintenance metoclopramide infusion lasted for only 8 hours[8]. The superior efficacy of intravenous ondansetron in the acute phase does not guarantee its favorite status in the delayed phase when taken orally, as revealed in this study. A recent review of available clinical trials in which oral ondansetron and oral metoclopramide were compared also showed that ondansetron was, at best, equal to metoclopramide in preventing nausea and vomiting induced by cancer chemotherapy[9]. Whether a poor enteral absorption led to unsatisfactory oral bioavailability of ondansetron awaits well designed pharmacokinetic study.

The most common reported adverse event associated with ondansetron therapy was headache, whereas diarrhea and restlessness were the most common adverse events associated with metoclopramide therapy[10]. Inthis study, diarrhea was found to have a significantly higher incidence in metoclopramide (46.2% vs 0% in ondansetron) while the occurrence rates of headache in ondansetron (7.7%) and restlessness in high-dose metoclopramide (7.7%) were rather low. Low incidence of extrapyramidal symptoms in high-dose metoclopramide in this study was compatible with a previous report that extrapyramidal reactions ocurred in 27.3% of patients aged 15 to 29 and in only 1.8% of patients aged 30 to 72[11].

In this study, ondansetron was found to be very effective and safe for control of nausea and emesis induced by cisplatin-based chemotherapy in aged patients with urogenital malignancy, especially in acute phase. However, for the purpose of comparison between ondansetron and high-dose metoclopramide, the study design permitted only a single antiemetic therapy for a single patient. This does not mean that any single antiemetic regimen would be good enough for control of chemotherapy-induced emesis. Combination of ondansetron with dexamethasone and chlorpromazine was recently found to be superior to ondansetron alone in the prevention of nausea and vomiting associated with cisplatin[12]. Possible benefit from combina-

tion of ondansetron with high-dose metoclopramide might deserve further investigation.

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於 Cisplatin 爲主之化學治療中 Ondansetron 與高劑量 Metoclopramide 預防嘔吐效果之比較

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背景：Cisplatin 經由 5-hydroxytryptamine (serotonin)之 5-HT_3接受器引起之噁心及嘔吐一直是癌症病人接受化學藥物治療中最嚴重副作用之一。一種 5-HT_3接受器之拮抗劑 Ondansetron 用前已經被研發作爲預防化學治療導致之噁心嘔吐之用，但在高年齡層之中國癌症病人身上，其藥效及副作用之資料尚屬欠缺，吾人遂進行 Ondansetron 與傳統化療標準止吐用藥之一的高劑量 Metoclopramide 之比較研究，研究進行之對象爲二十六位年齡在五十五歲以上之病人，這些病人皆因泌尿生殖系統之癌症而第一次接受含 Cisplatin 之化學藥物治療。

方法：根據病人主觀選擇分爲兩組，每組剛好十三人，每組各只接受 Ondansetron 或高劑量 Metoclopramide 其中之一作爲 Cisplatin 治療中唯一的止吐藥劑，在化學治療之第一天(急性期)，止吐藥係由靜脈給予，而自第二天至第六天(延續期)則以口服劑型給予，噁心及嘔吐之程度評估與記錄，係根據分級設計之評比表。

結果：於急性期，噁心及嘔吐之控制，經 Wilcoxon 分級加成檢驗顯示，Ondansetron 優於 Metoclopramide (P 值分別爲 0.008 及 0.013)，以達到完全沒有噁心或嘔吐方面來看，在 Fisher's 實情檢驗下，Ondansetron 亦處優勢(P 值分別爲 0.007 及 0.003)，可是在延續期方面，以 Wilcoxon 分級加成檢驗作單獨各天之比較，結果顯示第二天及第三天中抗嘔吐之效力 Ondansetron 及 Metoclopramide 兩者相等，而自第四天至第六天中，Metoclopramide 反優於 Ondansetron，治療過程中，腹瀉較常見於 Metoclopramide (46.2%)而不見於 Ondansetron (0%)，錐體外症候產生一例於 Metoclopramide (7.7%)而不見於 Ondansetron (0%)。

結論：使用 Cisplatin 爲主之化學藥物治療時，急性期噁心嘔吐之控制，在靜脈注射方式下，Ondansetron 優於 Metoclopramide，但在延續期之口服治療中，Ondansetron 不能優於 Metoclopramide。

關鍵詞：Ondansetron, Metoclopramide, 嘔吐，Cisplatin.

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