Comparison of Oral *versus* Intravenous Ramosetron in Prevention of Acute Cisplatin-Induced Emesis : A Randomized Controlled Trial

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Abstract

Objective : To compare the antiemetic efficacy of a single oral *versus* intravenous (IV) ramosetron, a new class of selective 5-HT_3 receptor antagonists, in gynecologic cancer patients receiving high-dose cisplatin.

Method : Between February 2003 and July 2003, 109 patients with gynecologic cancer scheduled to receive single agent cisplatin chemotherapy at a dose of 75 mg/m^2 were randomized to receive either 0.2 mg oral (51 cases) or 0.3 mg IV (58 cases) ramosetron 1 h and 30 min respectively before chemotherapy. Patients were evaluated for 24 h after chemotherapy. The number of nausea and vomiting including adverse events were recorded every 6 h.

Results : 51 and 58 patients received oral and IV ramosetron respectively. Both groups were similar regarding age, performance status, body mass index and diagnosis of gynecologic cancer. 95 per cent of cases were cervical cancer. Antiemetic effect was significantly higher in the oral group when compared with the IV group during the first 6 hours and during the period of 18 to 24 hours after administration of cisplatin chemotherapy. Overall in 24 h, patients receiving oral ramosetron experienced no emesis slightly higher than that of the IV group (55% and 36% respectively, $p = 0.05$). Adverse events were mild and transient and were not significantly different in both groups, except tiredness which was more frequent in the IV group.

Conclusion : Oral ramosetron at a dosage of 0.2 mg is as effective as 0.3 mg of intravenous ramosetron in prevention of acute emesis in patients receiving 75 mg/m^2 of cisplatin chemotherapy.

Key word : Ramosetron, Cisplatin, Chemotherapy, Antiemesis

**TANTIPALAKORN C,
SRISOMBOON J, THIENTHONG H, et al
J Med Assoc Thai 2004; 87: 119-125**

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Nausea and vomiting are the most frequent and unpleasant side effects associated with cancer chemotherapy. Cisplatin is regarded as the most emetogenic of all currently used chemotherapeutic agents, in which nearly all (> 99%) patients if not premedicated with antiemetics, are expected to vomit[1-3]. Cisplatin induces acute emesis with a latency period of about 2-4 hours and a peak incidence of 6-8 hours [4]. The dose of cisplatin also affects the severity of emesis. Conventionally low-dose cisplatin (< 50 mg/m^2) is considered moderately rather than severely emetogenic, which causes 60-90 per cent emesis[2]. There is evidence of a dose-response effect for cisplatin > 50 mg/m^2, with increasing nausea and vomiting at higher doses[5]. As the dose of cisplatin increases, the ability to control acute emesis decreases.

The type 3 serotonin or 5-hydroxytryptamine (5-HT_3) receptors in afferent vagus nerve fibers and in neurons of the gastrointestinal tract are involved in inducing acute emesis associated with cancer chemotherapy. During cisplatin chemotherapy, mucosal enterochromaffin cells are stimulated to release serotonin which binds to 5-HT_3 receptors in afferent vagus nerve terminals. This binding provokes the vomiting center, either directly or *via* 5-HT_3 receptors present in the chemoreceptor trigger zone, and induces vomiting[6,7]. Therefore, blockade of 5-HT_3 receptors in the small intestine by selective 5-HT_3 receptor antagonists might be effective in prevention of acute emesis following chemotherapy.

Ramosetron (Nasea®, Yamanouchi Pharmaceutical Co. Ltd, Tokyo, Japan) a new class of selective 5-HT_3 receptor antagonists, has potent anti-emetogenic effects[8-10]. Its potency is higher and its antiemetic effect lasts longer than those of granisetron [11]. In evidence-based clinical practice guidelines, the combination of a 5-HT_3 antagonist plus a corticosteroid is recommended before cisplatin chemotherapy [12]. Since both oral and intravenous ramosetron given without corticosteroid are effective in prevention of emesis, no study has been conducted to compare the efficacy of both regimens in patients receiving high-dose cisplatin (75 mg/m^2). Accordingly, the present study was undertaken to compare the antiemetic efficacy of a single oral *versus* intravenous ramosetron in gynecologic cancer patients receiving high-dose cisplatin.

MATERIAL AND METHOD

From February 1, 2003 to July 31, 2003, one hundred and nine patients with gynecologic cancer scheduled to receive single agent cisplatin chemotherapy in Chiang Mai University Hospital were recruited into the study. Patients aged 20 to 70 years were eligible to participate in this study. They must have no contraindication to cisplatin and serotonin antagonists, and have adequate renal, bone marrow and liver functions. Patients were excluded from the study if they had complications of diseases that could cause vomiting, e.g. bowel obstruction or were pregnant. All patients provided written informed consent prior to participation in the study.

Cisplatin at a dose of 75 mg/m^2 was administered as a single intravenous (IV) infusion over 4 hours. Patients were allocated to receive either oral or IV ramosetron by block randomization. Oral ramosetron (0.1 mg) 2 tablets were given 1 hour before cisplatin chemotherapy. Intravenous ramosetron 0.3 mg was administered 30 minutes before cisplatin administration.

Patient characteristics including age, height, body weight, body mass index, performance status defined by the Eastern Co-operative Oncology Group (ECOG)[13], diagnosis, underlying disease and complications were recorded at enrollment. Patients were evaluated for 24 hours after the start of cisplatin infusion. The time and amount of nausea and vomiting were recorded every 6 hours. Antiemetic efficacy was graded as follows: grade 0 (no emesis), grade 1 (1 emetic episode), grade 2 (2 to 5 emetic episodes), and grade 3 (≥ 6 emetic episodes or need IV fluid). Nausea were graded as follows; grade 0 (no nausea), grade 1 (mild nausea but able to take solid foods and fluids), grade 2 (moderate nausea able to take only fluids), and grade 3 (severe nausea, unable to eat).

All adverse events were recorded. Standard laboratory tests including hematologic profiles, renal and liver function test were performed before ramosetron administration. Vital signs, i.e. body temperature, blood pressure, pulse rate, and respiratory rate were measured both before and 24 hours after ramosetron administration. Patients with abnormal findings were monitored until the signs returned to normal.

Data analysis comparing clinical characteristics, safety and antiemetic efficacy between the oral and IV ramosetron was carried out using the Chi square test. Comparison of mean values between groups was performed using the Student *t*-test. P-value of less than 0.05 was judged statistically significant.

RESULTS

Among the 109 patients, 51 and 58 were randomized to receive oral and intravenous ramosetron

respectively. The age of the patients, performance status and body mass index were similar in both groups as shown in Table 1. Most of the patients had cervical cancer and received single agent cisplatin chemotherapy in a neoadjuvant or an adjuvant setting. Patients with ovarian cancer or vulvar cancer received cisplatin as adjuvant chemotherapy after the operation.

In the first 6 hours after administration of cisplatin chemotherapy, no emesis occurred in 92.1 per cent and 77.6 per cent of patients in the oral and the IV groups respectively; this difference was statistically significant. During the period of 6 to 18 hours after cisplatin, the proportion of patients who experienced no emesis did not significantly differ in both groups. However, during the period of 18 to 24 hours after cisplatin, no emetic episode was noted significantly higher in the oral group when compared with that of the IV group as shown in Table 2. Overall, during the 24 hours following cisplatin administration, a complete prevention of emesis, i.e. grade 0 emesis, was found in 28 of 51 patients (55%) in the oral group and 21 of 58 patients (36%) in the IV group which was not significantly different ($p = 0.05$).

The effect of oral and IV ramosetron in prevention of nausea did not significantly differ between groups during each 6-hour period after the administration of cisplatin chemotherapy as shown in Table 3. Patients receiving oral ramosetron seemed to have grade 0 nausea slightly higher than those receiving IV ramosetron during the period of 12 to 24 hours after cisplatin.

Table 4 shows adverse events occurred in patients receiving oral and IV ramosetron. No serious side effect was found in both groups. All adverse events were mild and transient, and disappeared spontaneously without any medication. The most common adverse events in the oral group were heavy-headed sensation (27.5%), followed by dry mouth (17.6%),

Table 1. Clinical characteristics of the patients.

Characteristics	Oral (n = 51)	%	Intravenous (n = 58)	%
Age (yrs)				
Mean ± SD	41.73 ± 7.7		41.36 ± 8.2	
Range	27 - 58		25 - 65	
Performance status				
0	8	15.7	12	20.7
1	43	84.3	45	77.6
2	0		1	1.7
Body mass index				
Mean ± SD	23.1 ± 3.5		22.4 ± 3.7	
Range	15.5 - 35.2		15.4 - 35.0	
Diagnosis				
Cervical cancer	48	94.1	55	94.8
Ovarian cancer	1	2.0	2	3.5
Vulvar cancer	2	3.9	1	1.7

Table 2. Effects of oral and intravenous (IV) ramosetron on emesis.

Time after chemotherapy (h)	Route	Number of patients with emesis							
		Grade 0	%	Grade 1	%	Grade 2	%	Grade 3	%
0-6	Oral	47	92.1*	3	5.9	1	2.0	0	
	IV	45	77.6	9	15.5	3	5.2	1	1.7
6-12	Oral	38	74.5	6	11.8	7	13.7	0	
	IV	44	75.9	9	15.5	4	6.9	1	1.7
12-18	Oral	41	80.5	5	9.8	5	9.8	0	
	IV	40	69.0	10	17.2	7	12.1	1	1.7
18-24	Oral	39	76.5**	5	9.8	7	13.7	0	
	IV	30	51.7	17	29.3	11	19.0	0	

* P-value = 0.04 compared with IV ramosetron (Chi-square test).
** P-value = 0.007 compared with IV ramosetron (Chi-square test).

Table 3. Effects of oral and intravenous (IV) ramosetron on nausea..

Time after chemotherapy (h)	Route	Number of patients with nausea							
		Grade 0	%	Grade 1	%	Grade 2	%	Grade 3	%
0-6	Oral	38	74.5	10	19.6	3	5.9	0	
	IV	40	69.0	14	24.1	4	6.9	0	
6-12	Oral	30	58.8	14	27.5	7	13.7	0	
	IV	40	69.0	10	17.2	7	12.1	1	
12-18	Oral	25	49.0	18	35.3	8	15.7	0	
	IV	26	44.8	16	27.6	15	25.9	1	1.7
18-24	Oral	26	51.0	17	33.3	7	13.7	1	2.0
	IV	21	36.2	22	37.9	15	25.9	0	

Table 4. Adverse events of oral and intravenous ramosetron.

Adverse events	Oral (n = 51)	%	Intravenous (n = 58)	%	P-value
Heavy feeling in the head	14	27.5	13	22.4	0.5
A "hot body" sensation	2	3.9	4	6.9	0.5
Dry mouth	9	17.6	7	12.1	0.4
Headache	9	17.6	14	24.1	0.4
Facial flushing	0		1	1.7	0.3
Constipation	2	3.9	6	10.3	0.2
Numbness of tongue	0		1	1.7	0.3
Tiredness	0		6	10.3	0.02
Insomnia	4	7.8	5	8.6	0.8
Fever	5	9.8	6	10.3	0.9

and headache (17.6%). The most common adverse events in the IV group were headache (24.1%), followed by heavy-headed sensation (22.4%), and dry mouth (12.1%). Patients receiving IV ramosetron appeared to experience tiredness significantly more frequently than those receiving oral ramosetron. The other adverse events were not different in both groups.

DISCUSSION

The results of the present study showed that oral ramosetron at dosage of 0.2 mg administered 1 hour before chemotherapy was as effective as 0.3 mg of IV ramosetron in prevention of acute cisplatin-induced emesis. The dose of cisplatin chemotherapy used in this study was rather high at 75 mg/m^2. In our pilot study of 10 patients receiving 0.1 mg of oral ramosetron for prevention of vomiting, the authors found that 8 (80%) of these patients suffered from severe vomiting during the 24 hour period. Consequently, the dose of oral ramosetron was stepped up to 0.2 mg in the present study to compare with the IV ramosetron. The anti-emetic efficacy of the oral group was significantly higher than the IV group during the first 6 hours and during the period of 18 to 24 hours after cisplatin chemotherapy.

The anti-emetic efficacy of IV ramosetron during the 24 hour period after cisplatin chemotherapy in the present study was comparable to that of the study by Noda et al in which the dose of cisplatin varied from 40-120 mg/m^2[14]. No emesis occurred in 36 per cent in the present study comparable to 35 per cent in the study by Noda et al[14]. Since the incidence of emesis depends on dosage of cisplatin the authors could not compare the anti-emetic efficacy of oral ramosetron with the other study which used different doses of cisplatin. Taketani et al used oral ramosetron at a dose of 0.1 mg given 1 hour before administration of cisplatin in a single dose of 50 mg/m^2 or more. No vomiting was found in 48 per cent of the patients for 24 hours after chemotherapy, and 77.8 per cent had two or fewer times of vomiting[15].

No serious adverse events were noted in patients receiving either oral or IV ramosetron in the present study. All adverse events were mild and transient. The main adverse events in the oral group were

heavy-headed sensation, dry mouth and headache. In contrast, headache was the leading adverse event followed by heavy-headed sensation and dry mouth accounting for 24.1 per cent, 22.4 per cent, and 12.1 per cent respectively in patients receiving IV ramosetron. Feng et al reported their experience using IV ramosetron at the same dosage as in the present study and noted that heavy-headed sensation (10.7%), dry mouth (10.7%) headache (5.8%) and tiredness (5.8%) were the main adverse events[16]. The incidence of headache in the IV group in the present study was comparable to that of the study by Kang et al which reported an incidence of 22.3 per cent[17]. Approximately half of the adverse events in their study were evaluated as not drug-related[17].

In conclusion, oral ramosetron at a dosage of 0.2 mg is as effective as 0.3 mg of IV ramosetron in prevention of acute vomiting in patients receiving cisplatin chemotherapy at 75 mg/m^2 of dosage.

ACKNOWLEDGEMENT

The authors wish to thank Yamanouchi (Thailand) Co., Ltd. for providing ramosetron and other support for the clinical trial.

(Received for publication on November 5, 2003)

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การศึกษาเปรียบเทียบระหว่างการรับประทานกับการฉีดยารามอสซีตรอนเข้าหลอดเลือดดำ ในการป้องกันภาวะอาเจียนเฉียบพลันจากยาซิสพลาติน

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วัตถุประสงค์ : เพื่อเปรียบเทียบประสิทธิภาพของยารามอสซีตรอน (ซึ่งเป็นยากลุ่ม selective 5-HT_3 receptor antagonists) ระหว่างการรับประทานและการฉีดเข้าหลอดเลือดดำ ในผู้ป่วยมะเร็งทางนรีเวชที่ได้รับยาซิสพลาตินขนาดสูง

วิธีการ : ระหว่างกุมภาพันธ์ 2546 ถึงกรกฎาคม 2546, ผู้ป่วยมะเร็งทางนรีเวชจำนวน 109 ราย ซึ่งได้กำหนดให้รับเคมีบำบัดด้วยยาซิสพลาตินในขนาด 75 มก/ตารางเมตร ได้รับการสุ่มให้ได้รับยารามอสซีตรอนแบบรับประทาน 0.2 มก (51 ราย) หรือฉีดทางหลอดเลือดดำ 0.3 มก (58 ราย) ก่อนให้เคมีบำบัด 1 ชั่วโมงและ 30 นาทีตามลำดับ ผู้ป่วยได้รับการประเมินเป็นเวลา 24 ชั่วโมงหลังให้เคมีบำบัดและทำการบันทึกจำนวนครั้งของการคลื่นไส้และอาเจียน รวมถึงฤทธิ์ข้างเคียงทุก 6 ชั่วโมง

ผลการศึกษา : ผู้ป่วยได้รับรามอสซีตรอนชนิดรับประทานและฉีดจำนวน 51 และ 58 รายตามลำดับ ทั้งสองกลุ่มไม่มีความแตกต่างกันในแง่ของอายุ performance status, ดรรชนีมวลกายและชนิดของโรคมะเร็ง โดยร้อยละ 95 เป็นมะเร็งปากมดลูก ฤทธิ์ต้านอาเจียนในกลุ่มรับประทานสูงกว่ากลุ่มฉีดอย่างมีนัยสำคัญ ในช่วง 6 ชั่วโมงแรกและช่วง 18–24 ชั่วโมงหลังให้ยาซิสพลาติน โดยรวมแล้วใน 24 ชั่วโมง กลุ่มรับประทานมีจำนวนผู้ป่วยที่ไม่อาเจียนเลยสูงกว่ากลุ่มฉีดเล็กน้อย (ร้อยละ 55 และร้อยละ 36 ตามลำดับ, ค่าพี 0.05) ฤทธิ์ข้างเคียงอื่น ๆ มีเพียงเล็กน้อยและชั่วระยะเวลาสั้น ๆ และไม่มีความแตกต่างกันในทั้งสองกลุ่ม ยกเว้นความรู้สึกเหนื่อยเพลียจะพบในกลุ่มฉีดได้บ่อยกว่า

สรุป : การให้ยารามอสซีตรอนโดยวิธีรับประทานขนาด 0.2 มก มีประสิทธิภาพเท่ากับการให้แบบฉีดเข้าหลอดเลือด 0.3 มก ในแง่ของการป้องกันอาการอาเจียนเฉียบพลันในผู้ป่วยที่ได้รับยาซิสพลาติน 75 มก/ตารางเมตร

คำสำคัญ : รามอสซีตรอน, ซิสพลาติน, เคมีบำบัด, ยาต้านอาเจียน

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จดหมายเหตุทางแพทย์ ฯ 2547; 87: 119–125

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