Study of Efficacy and Tolerability of Tropisetron in the Prevention of Cisplatin Induced Nausea and Vomiting

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Abstract

The efficacy and tolerability of tropisetron alone or in combination with dexamethasone was studied in an open randomised trial in a total of 30 patients undergoing cisplatin based chemotherapy. Patients received tropisetron 5 mg plus dexamethasone 8 mg iv on day 1 followed by tropisetron 5 mg p.o. plus dexamethasone 4 mg orally bid on day 2-6 (group I) *versus* tropisetron 5 mg p.o. alone on day 2-6 (group II). No demographic difference among the groups was observed. Tumor locations were mainly at cervix (23%) and ovary (17%). Acute emesis was prevented completely, defined as no nausea and no vomiting, in 75 per cent of patients in group 1 compared with 73 per cent in group II. Delayed emesis was completely prevented in significantly more patients in group I (81% *versus* 49%). Adverse events were mild and similar in both groups. The most frequent side effects were headache, stupor and diarrhea. In conclusion, tropisetron is an effective and well tolerated antiemetic for preventing acute and delayed emesis in cisplatin-based chemotherapy. In addition, combining dexamethasone improved the efficacy in particular in controlling delayed emesis.

Key word : Tropisetron, Efficacy, Tolerability, Prevention, Cisplatin Induced Nausea and Vomiting

$5HT_3$ receptor antagonists are now confirmed to be effective by many clinical studies in the prevention and treatment of chemotherapy induced nausea and vomiting.

Tropisetron, one of the $5HT_3$ receptor antagonists, acts by inhibiting both peripheral and central $5HT_3$ receptors, thereby interrupting the vomiting reflex[1]. Tropisetron has proved to be more effective than metoclopramide in preventing acute chemotherapy-induced vomiting[2,3]. Its success is remarkable even in patients receiving high dose cisplatin[4]. It is especially potent in the prevention of acute vomiting[2,3,5] ; delayed nausea and vomiting[2]. In addition it is also effective in

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cases where conventional antiemetics have proven ineffective[5] and has been shown to maintain its efficacy over several cycles of chemotherapy[6]. Tropisetron (Navoban®) is one of the anti-emetic agents that is efficacious, simple to administer, and well tolerated by most patients.

This study was performed to evaluate the antiemetic efficacy of tropisetron compared with the combination of tropisetron and dexamethasone in the prevention of acute and delayed emesis induced by a cisplatin based regimen. Safety and tolerability were also assessed.

PATIENTS AND METHOD

Patients

From May to December 1996 twenty-seven patients aged over 18 years with a variety of malignancies were enrolled in the study. Forty per cent of the patients were male and 60 per cent were female. Patients were treated with various different chemotherapeutic regimens which comprised of cisplatin at the dose of >100 mg/m^2 and other anticancer agents (Table 3). There was no demographic difference between the 2 groups in respect to gender, age and tumor type (Table 1 and Table 2).

Patients with evidence of malignancy involving the CNS, current severe hepatic or cardiac insufficiency, uncontrolled infection, drug or alcohol abuse, hypersensity reaction, drug allergy, pregnancy or child bearing potential without appropriate birth control method were excluded. Before participating in the study, all patients gave informed consent. They were free to withdraw at any time.

Antiemetic Treatment

The study was of open randomised design. Patients were treated with tropisetron 5 mg and dexamethasone 8 mg, administered intravenously shortly before chemotherapy on day 1. Thereafter, on day 2 to 6, patients who had been randomised into group 1 received tropisetron 5 mg oral capsule at least 1 hour before a meal and dexamethasone 4

Table 1. Demographics of the patients.

Demographics		Tropisetron			
		Group I		Group II	
		No.	%	No.	%
Total		16	100	14	100
Evaluable		14	87.5	13	92.88
Sex	Male	5	35.71	6	46.15
	Female	9	64.28	7	53.86
Age (years)	Range	23-68		30-69	
	Average	51.69		49.69	

Table 2. Histological diagnosis.

Type of cancer	Group I	%	Group II	%
Cervix	4	28.57	3	23.07
Ovary	2	14.28	3	23.07
Lower Gum, Lip	2	14.28	2	15.38
Esophagus	-	-	3	23.07
NPC	3	21.42	-	-
Lung	1	7.14	1	7.69
Nasal canal	1	7.14	-	-
Testis	-	-	1	7.69
Anus	-	-	1	7.69
Stomach	1	7.14	-	-

Table 3. Regimens for treating each type of cancer.

Type of cancer	Regimen
Cervix	EP.
Ovary	PAF., ExP., Taxol P.
Lower Gum, Lip	PF.
Esophagus	PF.
NPC	PF.
Lung	PVB.
Nasal canal	PF.
Testis	PVB.
Anus	PF.
Stomach	PF.

E = Epirubicin
Ex = Cyclophosphamide
V = Vinblastine
P = Cisplatin
A = Adriamycin
F = 5-Fluorouracil
B = Bleomycin

Table 4. Efficacy criteria on day 1-6.

	Control of vomiting	Control of nausea
o complete control	0	0
o partial control		
- major control	1-2	1-2
- minor control	3-4	3-4

mg orally daily, while patients in group II received only tropisetron 5 mg oral capsule.

Assessment

The purpose of this study was to evaluate the efficacy in controlling acute (day 1) and delayed (day 2-6) emesis. Vomiting and retching were recorded as the number of separate events. Nausea was recorded every hour within a 24 hour period. A single episode of nausea was defined as one "clock hour" in which nausea occurred regardless of the exact duration or severity of nausea. Complete control was defined as no nausea and vomiting, partial control as 1-4 episodes of vomiting or 1-4 episodes of nausea in the same period, and treatment failure as 5 or more episodes of vomiting or nausea. Control of nausea and vomiting was analysed both over a 24 hour period and for each of 5 days.

Blood samples for hematology and biochemistry were taken before and at the end of treatment. After starting the chemotherapy on day 1, the supine BP, heart rate, body temperature, number of vomiting episodes and severity of nausea were recorded every 8 hours on the nursing chart. Adverse events were recorded by the investigators and collected from the patients' diaries.

Table 5. Intensity of acute emesis on Day 1 (During 24 h post chemotherapy) Group I.

Response	First 12 h period		Second 12 h period		Total within first 24 h
	No.	%	No.	%	%
Complete response	11	78.57	10	71.42	75
Major response	2	14.28	3	21.42	17.86
Minor response	-	-	-	-	-
Failure	1	7.14	1	7.14	7.14

n = 14

Table 6. Intensity of acute emesis on Day 1 (During 24 h post chemotherapy) Group II.

Response	First 12 h period		Second 12 h period		Total within 24 h period
	No.	%	No.	%	%
Complete response	10	76.92	9	69.23	73.08
Major response	2	15.38	2	15.38	15.38
Minor response	-	-	1	7.69	3.85
Failure	1	7.69	1	7.69	7.69

n = 13
Complete response: No nausea and no vomiting, Major response: 1-2 emetic episodes
Minor response: 3-4 emetic episodes, Failure: 5 or more emetic episodes

Statistical Analysis

All main outcome variables (characteristics of patients, histological diagnosis, type of chemotherapeutics, efficacy and tolerability) were studied by means of the X2 test.

RESULTS

The 27 patients (11 male and 16 female) who were enrolled into the study were well-balanced for characteristics and histological diagnosis.

Table 5 shows the efficacy of tropisetron in controlling acute emesis in patients who received tropisetron and dexamethasone. Seventy-five per cent of the patients had a complete response, 17.86 per cent a major response, 0 per cent a minor response and 7.14 per cent failure while the efficacy in controlling delayed emesis was 81.16, 10.14, 1.45 and 7.14 per cent respectively. (Table 7)

In patients receiving tropisetron alone, group II, acute / delayed emesis could be controlled completely in 73.08 per cent / 49.23 per cent. Major response was 15.38 per cent / 29.23 per cent, minor response 3.85 per cent / 13.85 per cent and failure 7.69 per cent equally. (Table 6, 8)

The percentage of controlling acute and delayed emesis in both groups was not different. In group I, a complete response in delayed emesis seemed to be more pronounced and improved than group II.

Table 7. Intensity of delayed emisis (Day 2-6) Group I.

Response	Day 2		Day 3		Day 4		Day 5		Day 6		Mean
	No	%	No	%	No	%	No	%	No	%	%
Complete response	9	69.23	10	71.43	12	85.71	12	85.71	13	92.86	81.16
Major response	2	15.38	3	21.43	1	7.14	1	7.14	-	-	10.14
Minor response	1	7.69	-	-	-	-	-	-	-	-	1.45
Failure	1	7.69	1	7.14	1	7.14	1	7.14	1	7.14	7.25

n = 14, one patient did not come to the site on day 2.

Table 8. Intensity of delayed emisis (Day 2-6) Group II.

Response	Day 2		Day 3		Day 4		Day 5		Day 6		Mean
	No	%	No	%	No	%	No	%	No	%	%
Complete response	7	53.84	6	46.15	6	46.15	6	46.15	7	53.84	49.23
Major response	3	23.07	2	15.38	5	38.46	5	38.46	4	30.76	29.23
Minor response	2	15.38	4	30.76	1	7.69	1	7.69	1	7.69	13.85
Failure	1	7.69	1	7.69	1	7.69	1	7.69	1	7.69	7.69

n = 13

Table 9. Adverse events.

Description of adverse events	Group I		Group II	
	No.	%	No.	%
Headach	1	7.14	3	21.42
Diarrhea	2	14.28	1	7.14
Stupor	3	21.42	2	14.28
Cough	1	7.14	1	7.14
Itching (erythema)	0	0	2	14.28
Tightness	1	7.14	2	14.28
Total	8	57.14	11	78.57

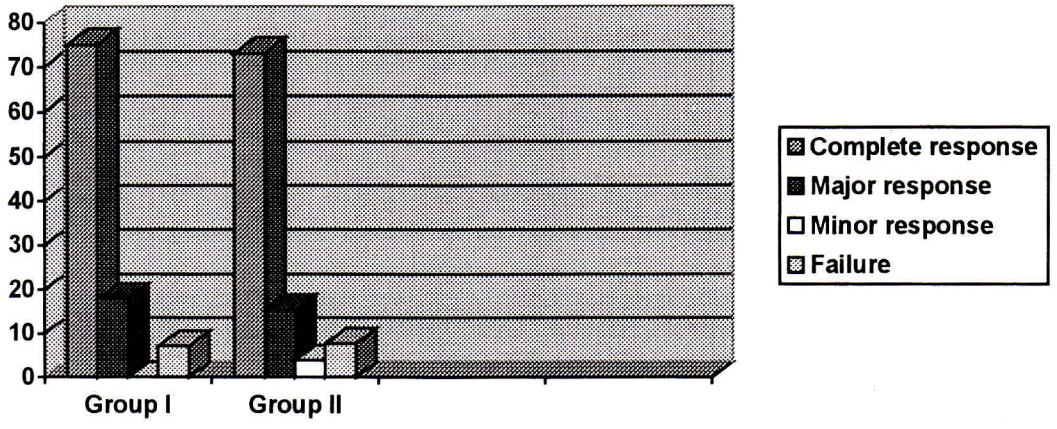

Fig. 1. Intensity of acute emesis Group I & II.

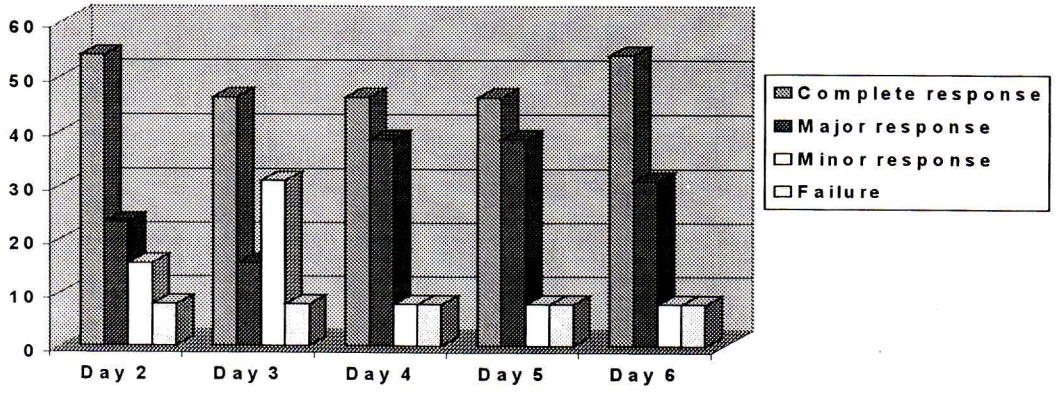

Fig. 2. Intensity of delayed emesis Group I.

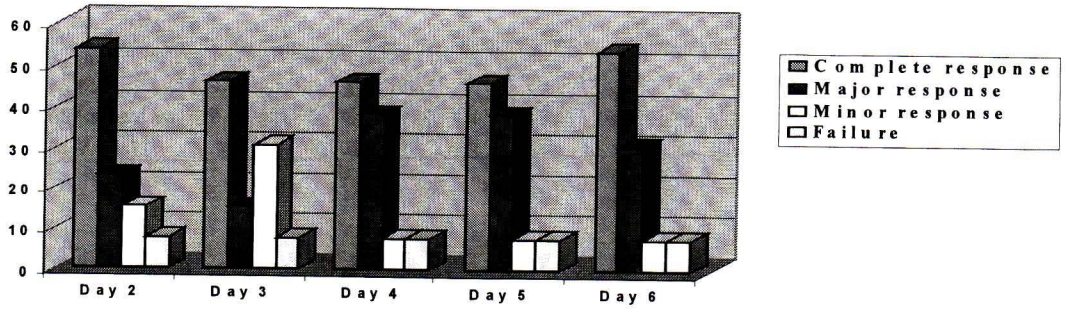

Fig. 3. Intensity of delayed emesis Group II.

Tropisetron was well tolerated. Adverse effects were mild and did not require to be treated. The most frequent reported events during the whole study were stupor (5 patients), headache (4 patients) and diarrhea (3 patients).

DISCUSSION

In this study, the efficacy of tropisetron alone and tropiseton plus dexamethasone was tested in 27 Thai patients. The results show that tropisetron, alone or in combination, is an effective antiemetic treatment during a cisplatin based regimen. Tropisetron alone can control emesis in both acute and delayed periods with a high percentage of response. However, as with other $5HT_3$ receptor antagonists, it is likely that the therapeutic effect of combination regimen including dexamethasone was more effective and significantly improved the control of delayed emesis than a single agent.

Complete control of acute emesis in group I *versus* group II was 75 per cent *versus* 73.08 per cent (Fig. 1).

Complete control of delayed emesis was attained in 81.16 per cent of group I but in only 49.23 per cent of group II and improved control of emesis was much more marked in group I than the other group (69.23% to 92.86%) from day 2-6 *versus* 53.84 per cent (Fig. 2 and 3). Although the percentage of complete control delayed emesis in patients receiving tropisetron and dexamethasone was higher than those receiving tropisetron alone, the percentage of failure in both groups was not significantly different (Fig. 2, 3).

The main side effects reported were stupor, headache and diarrhea which are known side effects of $5HT_3$ receptor antagonists. The difference between the treatment groups in the side effects was no longer statistically significant or clinically relevant (Table 9).

In conclusion, tropisetron 5 mg od., is an effective, well tolerated and simple to use drug for preventing acute and delayed emesis in patients receiving cisplatin-based chemotherapy. The addition of dexamethasone enhances the effectiveness of tropisetron and gives significant benefit with good toleration in controlling delayed emesis.

(Received for publication on December 29, 1998)

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ผลการศึกษาประสิทธิผล, ความปลอดภัยและผลข้างเคียงของยาซึ่งเกิดกับผู้ป่วยที่ได้รับยาโทรพิเสตรอน ในการป้องกันอาการคลื่นไส้–อาเจียน แบบเฉียบพลันที่เกิดจากยาเคมีบำบัด

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ช่วงเวลาตั้งแต่ 13 พฤษภาคม 2539 ถึง 31 ธันวาคม 2539 กลุ่มงานเคมีบำบัดสถาบันมะเร็งแห่งชาติ กรมการแพทย์ กระทรวงสาธารณสุข ได้ทำการศึกษาประสิทธิผล, ความปลอดภัย และผลข้างเคียงของยา ที่เกิดกับผู้ป่วยที่ได้รับยา Tropisetron (NAVOBAN) ในการบำบัดอาการคลื่นไส้ อาเจียนแบบเฉียบพลันที่เกิดจากการได้รับยาเคมีบำบัด

จำนวนผู้ป่วยที่ทำการศึกษามีทั้งสิ้น 30 คน (ประเมินผล 27 คน) ได้รับยา Tropisetron 5 mg ร่วมกับ Dexamethasone 8 mg ทางเส้นเลือดดำ ก่อนการให้ยาเคมีบำบัดในวันแรก และรับประทานยาต่ออีก 5 วัน โดยในการให้ยา 5 วันหลังนี้ได้แบ่งผู้ป่วยเป็น 2 กลุ่ม กลุ่มที่ 1 ให้รับประทาน Tropisetron 5 mg ก่อนอาหารเช้า 1 ชั่วโมง ร่วมกับรับประทาน Dexamethasone 4 mg 2 ครั้ง หลังอาหาร เช้า, เย็น กลุ่มที่ 2 ให้รับประทาน เฉพาะ Tropisetron 5 mg ก่อนอาหารเช้า 1 ชั่วโมง

ผลการป้องกันอาการคลื่นไส้อาเจียน ประเมินได้ 2 ระยะ คือ แบบเฉียบพลัน (อาการคลื่นไส้อาเจียนที่เกิดขึ้นภายใน 24 ชั่วโมงหลังจากได้รับยาเคมีบำบัด) และแบบ Delay (อาการคลื่นไส้อาเจียนหลังจากได้รับยาเคมีบำบัดแล้ว 2–6 วัน)

พบว่า ยา Tropisetron (NAVOBAN) มีประสิทธิภาพในการบำบัดอาการคลื่นไส้และอาเจียน ชนิดเฉียบพลัน และ Delay อันเป็นผลข้างเคียงของยาเคมีบำบัด โดยเฉพาะกลุ่มยาเคมีบำบัดที่ทำให้เกิดอาการคลื่นไส้อาเจียนที่รุนแรง ได้แก่ ยา Cisplatin ได้ผลดี คิดเป็นร้อยละ 73 และ 49 ตามลำดับ และประสิทธิภาพของยา Tropisetron ในการบำบัดอาการคลื่นไส้อาเจียนได้ผลดียิ่งขึ้นเมื่อใช้ร่วมกับ Dexamethasone ซึ่งได้ผลดีคิดเป็นร้อยละ 75 และ 81 ตามลำดับ

ผลข้างเคียงที่พบ เช่น ปวดศีรษะ, ท้องเสีย, มึนงง, แน่นหน้าอก, ผื่นคัน ประมาณร้อยละ 7–20 อาการดังกล่าวไม่รุนแรง ไม่ต้องได้รับการบำบัดรักษาพิเศษในผู้ป่วยมะเร็งที่ทำการศึกษานี้

คำสำคัญ : โทรพิเสตรอน, ประสิทธิผล, ความทนต่อยา, การป้องกัน, อาการคลื่นไส้–อาเจียนจากเคมีบำบัด

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