Phase II Trial of Tropisetron and Dexamethasone in the Prevention of Cisplatin-Induced Emesis

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Abstract

Thirty-one patients treated with 58 cycles of cisplatin-based chemotherapy at a dose > 80 mg/m^2 were enrolled into the study using tropisetron and dexamethasone in the prevention of cisplatin-induced emesis. There was 87.9 per cent complete control, 10.3 per cent major control, and 1.7 per cent failure for nausea episode on the first day of cycle. For the vomiting control, there was 96.6 per cent complete control, 3.4 per cent major control, and no failure. After the second day, the percentage of complete control increased gradually for both nausea and vomiting. The complete control for acute nausea and vomiting was 85.7 per cent and 92.9 per cent, respectively. The efficacy for delayed emesis was lower. There was 76.4 per cent complete control for delayed nausea and 85.7 per cent for delayed vomiting. The treatment was well tolerated without any serious adverse events related to tropisetron. Only hiccups was reported in 4 patients and recovered spontaneously at the end of the cycle. Combination of tropisetron and dexamethasone is an effective and safe antiemetic regimen in the prevention of cisplatin-induced emesis.

Key word : Tropisetron, Dexamethasone, Cisplatin-Induced Emesis

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J Med Assoc Thai 2000; 83: 668-675

Nausea and vomiting are common complaints of cancer patients, whether related to active treatment with chemotherapy or radiotherapy or arising at the terminal stage of the disease. Being placed in the number one adverse effects of systemic treatment, nausea and vomiting lead to a lasting impairment of the patient's quality of life, even during the treatment-free interval[1]. In the worst

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cases, the patients will decide to withdraw treatment before the course of chemotherapy is completed[2]. Thus, the successful control of nausea and vomiting induced by chemotherapeutic agents has become a crucial subject.

Many chemotherapeutic agents can cause nausea and vomiting. The degree to which these effects occur can vary, depending on the substance and the dose, from mild discomfort to severe vomiting for several hours under high-dose treatment with cisplatin. Conventional antiemetic substances, however, are often insufficiently effective and are attended by pronounced side effects. Frequently several medicines are used in an attempt to increase efficacy. This leads to a further increase in the incidence of side effects[3]. For these reasons, there has been an attempt to illustrate the mechanism of chemotherapy-induced emesis, in order to develop novel antiemetics.

Many studies have been carried out for this purpose and shown the linkage between 5-HT_3 receptor and chemotherapy-induced emesis. In animal models, the administration of cisplatin caused the release of serotonin (5-HT) in the small intestine to increase[4,5]. Both peripheral and central 5-HT_3 receptors have been indentified.

The highest concentration of 5-HT_3 receptors is located in the area postrema[6,7]. A high proportion of 5-HT_3 receptors have also been detected in the solitary nucleus, in the vagus nerve, and the nucleus of the spinal trigeminus. After 5-HT molecules were released from the enterochromaffin cells resulting from the stimulation by cytotoxic substance, they activated 5-HT_3 receptors in the submucosa of the GI tract and transmitted their impluses *via* afferent vagal nerves to the vomiting center (VC). A small amount of 5-HT was absorbed into the circulation and activated 5-HT_3 receptors in the chemoreceptor trigger zone (CTZ).

The nerve impluse from CTZ also activated VC. Neural stimulation of the VC, mostly *via* vagal nerve, cross a threshold valve, and the vomiting reflex is triggered[8-13]. According to this mechanism, the 5-HT_3 receptor antagonists were developed to block both peripheral and central afferent pathways of emesis.

Tropisetron is one of the selective 5-HT_3 antagonists that can prevent emesis due to chemotherapy especially cisplatin[14-22]. This phase II study was undertaken to evaluate the efficacy and safety of tropisetron in combination with dexamethasone in the prevention of cisplatin-induced emesis.

PATIENTS AND METHOD

Patient Selection

From July, 1996 to April, 1998, adult cancer patients who received cisplatin at doses $\geq$ 80 mg/m^2, were enrolled into the study. Written informed consent was obtained Cisplatin was administered only on the first day of cycle, either alone or in combination with other chemotherapeutic agents. On day 2-6 either no chemotherapy or only agents with low emetic potential were administered: 5-fluorouracil, UFT, etoposide and adriamycin.

Anti-emetic treatment

The treatment consisted of 5 mg of tropisetron intravenously (IV) and 20 mg of dexamethasone(IV), before cisplatin on day 1. On day 2-6, the patients received oral tropisetron, 5 mg daily in the morning, plus oral dexamethasone, 10 mg twice daily on days 2-6.

Clinical and laboratories assessment

Before the start of treatment in each cycle a full blood count, liver and kidney function tests were done. Those laboratories tests were repeated on day 6. All adverse reactions were recorded.

Control of nausea and vomiting was rated using a global assessment of antiemetic effect at the end of a 24 hour period each day in the treatment cycle. Complete control was defined as absence of episode, major control as one or two episodes, minor control as three or four episodes, and failure as five or more episodes.

Statistical Analysis

The pair T-test was used to compare pre and post treatment laboratories results. The antiemetic efficacy was expressed in percentage, mean and range of emetic episode.

RESULT

Thirty-one patients were given 58 cycles of treatment. Fourteen patients had received previous chemotherapy of 1-2 cycles. Twenty patients had received radiotherapy. There were 20 males and 11 females with a mean age of 48.2 $\pm$ 13.6 years (22-69). One patient recieved 5 cycles, 4 received 4,2 received 3,7 received 2, and the remaining patients received 1 cycle of tropisetron. The most common malignancy in this study was head and neck cancer (61.3%), followed by lung cancer (22.6%) (Table. 1).

Table 1. Patients characteristic.

-Number of patients	31
-Sex	
male	20(64.5)
female	11(35.5)
-Age	
Mean ± SD	48.2 ± 13.6
Range	22-69
-Primary cancer	
Head and Neck	19(61.3)
Lung	7(22.6)
Head and Neck and Lung	1 (3.2)
Liver	1 (3.2)
Others	3 (9.7)
-Previous chemotherapy	14(45.2)
-Radiotherapy	10(33.3)
-Metastasis site	
No	15(48.4)
Bone	2 (6.5)
Lung	1 (3.2)
Bone+Liver	1 (3.2)
Not evaluated	12(38.7)

Adverse Events

No serious adverse events related to tropisetron occurred. Hiccups was reported in 4 patients and spontaneously recovered by the end of the cycle. There was no complaint about headache and constipation in our patients. The laboratory results are shown in Table 1. When comparing cycle 1 to cycle 2, it is only the sodium level that has persistent significant difference in pre and post treatment results. However, those results were within normal range.

Treatment Efficacy

A total of 31 patients were included in the study. Three patients were excluded before analysis due to unexpected additional treatment with other antiemetic drugs.

Response was evaluated for up to five cycles of treatment. The antiemetic efficacy of this antiemetic regimen was analysed according to degree of achievement in each day of treatment cycle. We emphasized on both acute emetic control and delayed emetic control. To evaluate the persistence of antiemetic efficacy we evaluated the results in every cycle of treatment for each patient.

For all 58 cycles of treatment, there were 87.9 per cent complete control, 10.3 per cent major control and 1.7 per cent failure for nausea episode on the first day of cycle. The mean number of nausea episode was 0.21 ± 0.71 (range 0-5). For the vomiting control on the first day, there was 96.6 per cent complete control, 3.4 per cent major control, and no failure. The mean number of vomiting episodes was 0.05 ± 0.29 (range 0-2). On the second day of cycle, the percentage of complete control was 50.1 per cent for nausea episode and 72.4 per cent for vomiting episode. The percentage of major control was 31.0 per cent for nausea episode and 13.8 per cent for vomiting episode. There was 3.4 per cent minor control for both nausea and vomiting episode. The failure rate was 15.5 per cent for nausea episode and 10.3 per cent for vomiting episode. The mean number of episodes was 2.6 ± 5.51 (range-0-24) for nausea and 1.8 ± 6.30 (range 0-40) for vomiting. After the second day, the percentage of complete control increased day by day for both nausea and vomiting episode. (Table 2 and 3)

We divided the antiemetic efficacy of tropisetron into acute and delayed antiemetic control reported in each cycle of treatment. For acute emesis, there was only 1 case of failure for nausea control in cycle 3 and there was no failure in vomiting control. The complete control for acute nausea and vomiting was 85.7 per cent and 92.9 per cent at least (Table 4 and 5). There was less antiemetic efficacy for delayed emetic control as shown in Table 6 and 7.

Table 2. Efficacy on the control of nausea according to treatment day : (all cycles).

Nausea	Day 1 N=58	Day 2 N=58	Day 3 N=58	Day 4 N=58	Day 5 N=58	Day 6 N=58	Total N=345
Complete Control	51(87.9)	29(50.0)	46(79.3)	53(91.4)	57(95.3)	56(96.6)	292
Major Control	6(10.3)	18(31.0)	7(12.1)	4(9.6)	-	-	35
Minor Control	-	2(3.4)	5(8.6)	1(1.7)	1(1.7)	2(3.4)	11
Fail Control	1(1.7)	9(15.5)	-	-	-	-	10
X ± SD	0.21±0.74	2.6±5.51	0.5±1.05	0.14±0.51	0.07±0.53	0.14±0.74	-
Range	0-5	0-24	0-4	0-3	0-4	0-4	-

Table 3. Efficacy on the control of vomiting according to treatment day : (all cycles).

Vomiting	Day 1 N=58	Day 2 N=58	Day 3 N=58	Day 4 N=58	Day 5 N=58	Day 6 N=58	Total N=345
Complete Control	56(96.6)	42(72.4)	51(87.9)	57(98.3)	57(98.3)	58(100.0)	321
Major Control	2(3.4)	8(13.8)	4(9.6)	1(1.7)	-	-	15
Minor Control	-	2(3.4)	3(5.2)	-	1(1.7)	-	6
Fail Control	-	6(10.3)	-	-	-	58(100.0)	6
X ± SD	0.05±0.29	1.8±6.30	0.24±0.78	0.02±0.13	0.07±0.53	-	-
Range	0-2	0-40	0-4	0-1	0-4	-	-

Table 4. Efficacy on the control of acute emesis (nausea).

Nausea	Cr1	Cr2	Cr3	Cr4	Cr5
Complete Control	24(85.7)	12(85.7)	7(87.5)	5(100.0)	3(100.0)
Major Control	4(14.3)	2(14.3)	-	-	-
Minor Control	-	-	1(12.5)	-	-
Total	28(100.0)	14(100.0)	8(100.00)	5(100.0)	3(100.0)

Table 5. Efficacy on the control of acute emesis (vomiting).

Nausea	Cr1	Cr2	Cr3	Cr4	Cr5
Complete Control	26(92.9)	14(100.0)	8(100.0)	5(100.0)	5(100.0)
Major Control	2(7.1)	-	-	-	-
Total	28(100.0)	14(100.0)	8(100.0)	5(100.0)	3(100.0)

Table 6. Efficacy on the control of delayed emesis (nausea).

Nausea	Cr1	Cr2	Cr3	Cr4	Cr5
Complete Control	107(76.4)	60(85.7)	37(92.5)	24(96.0)	13(86.7)
Major Control	20(14.3)	4(5.7)	2(5.0)	1(4.0)	2(13.3)
Minor Control	7(5.0)	4(5.7)	-	-	-
Fail	5(4.3)	2(2.9)	1(2.5)	-	-
Total	140(100.0)	70(99.8)	40(100.0)	25(100.00	15(100.0)

In cycle 1 the overall complete control rate was 76.4 per cent for delayed nausea and 85.7 per cent for delayed vomiting. The percentage of complete control increased in subsequent cycles due to the drop out of failure cases after cycle 1.

DISCUSSION

Clinical trials with the 5-HT_3 receptor antagonists granisetron, ondansetron, tropisetron[23-25] have shown these agents to be effective antiemetic drugs. In additon, the combination of the5-HT_3

Table 7. Efficacy on the control of delayed emesis (vomiting).

Nausea	Cr1	Cr2	Cr3	Cr4	Cr5
Complete Control	120(85.7)	67(95.7)	39(97.5)	25(100.0)	14(93.3)
Major Control	9(6.4)	2(2.9)	1(2.5)	-	1(6.7)
Minor Control	5(3.6)	1(1.4)	-	-	-
Fail	6(4.3)	-	-	-	-
Total	140(100.0)	70(100.0)	40(100.0)	25(100.0)	15(100.0)

antagonist with dexamethasone in the prophylaxis of acute emesis caused by cisplatin has shown more effectiveness compared to 5-HT_3 anta-gonists alone (26-31). This combination of 5-HT_3 antagonists and a corticosteroid should be considered the "standard of care" for prevention of chemotherapy induced emesis, especially in the acute phase(32). In this present phase II trial, we achieved 85.7 per cent and 92.9 per cent complete control of nausea and vomiting consecutively within the first 24 hours of the treatment cycle. This result showed vomiting to be more easily controllable than nausea. The subsequent cycles seem to be under better control because the failure cases were dropped from the trial. This antiemetic regimen provided satisfactory results with respect to control of acute emesis.

However, delayed emesis remains an unsolved problem(32). As the results of our study show, the failure pattern of this antiemetic regimen was more profound in the delayed phase. In nine of ten failure cycles for nausea, uncontrolled nausea started on day 2. However, in only one cycle did uncontrolled nausea start within the first day. To date, there is no really effective treatment for the control of delayed nausea and vomiting. Dexamethasone or metoclopramide alone are of little value(33). The combination of both is superior to either dexamethasone alone or placebo(33,34). Tropisetron alone has a significant but limited activity in the prevention of delayed emesis. However, combination with dexamethasone also leads to a significant enhancement of efficacy in delayed symptoms, whereas, the addition of dopamine antagonists does not show any substantial effect(35-37). In conclusion, about delayed emesis control in our study, the percentage of complete control by tropisetron plus dexamethasone was 76.4 per cent for nausea control, and 85.7 per cent for vomiting control.

The adverse effects of the 5-HT_3 antagonist were generally mild. The common events were headache and constipation. But in our study there was no significant complaint about those particular events, propably because those events were overlooked by the patients. No significant abnormalities in hematology, renal and liver function were found. The only propable drug-related side effect in our study was hiccups in 4 patients. It persisted for 1-2 days and disappeared without any treatment. There was no report of hiccups in other studies or about the safety of 5-HT_3 antagonist (38-45). There were only some serious side effects(41-43) such as thrombotic episode, thombocytopenia and renal isufficiency,(44,45) reported in the studies of ondansetron.

In conclusion, our study revealed that the combination of tropisetron and dexamethasone was well tolerated and effective in preventing both acute and delayed cisplatin induced emesis. However, further studies to maximize the control of delayed emesis are warranted.

ACKNOWLEDGEMENT

This work was supported in part by Novartis Thailand Limited.

(Received for publication on August 11, 1999)

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การศึกษาระยะ 2 ของยาโทรปิเซตรอน และเด็กซาเมธาโซน ในการป้องกันการคลื่นไส้อาเจียนจากยาเคมีบำบัด

นรินทร์ วรวุฒิ, พ.บ., หฤษฎ์ สุวรรณรัศมี, พ.บ.**

ผู้ป่วยมะเร็งจำนวน 31 ราย ที่รักษาด้วยยาเคมีบำบัดซีสพลาติน ขนาด 80 มิลลิกรัมหรือมากต่อตารางเมตร จำนวน 85 ครั้ง ได้รับยาโทรปิเซตรอนและเด็กซาเมธาโซนในการป้องกันการคลื่นไส้อาเจียนจากยาเคมีบำบัดซีสพลาติน พบการควบคุมอาการคลื่นไส้อาเจียนแบบสมบูรณ์ร้อยละ 87.9 ป้องกันมากร้อยละ 10.3 และล้มเหลวร้อยละ 1.7 ในวันแรกของการให้ยา ป้องกันการอาเจียนแบบสมบูรณ์ร้อยละ 96.6 ป้องกันมากร้อยละ 3.4 และไม่มีการล้มเหลวหลังจากวันที่สองร้อยละของการควบคุมแบบสมบูรณ์เพิ่มมากขึ้นตามลำดับสำหรับการป้องกันอาการคลื่นไส้และอาเจียน อัตราการป้องกันการคลื่นไส้อาเจียนเฉียบพลันพบร้อยละ 85.7 และ 92.2 ตามลำดับประสิทธิภาพในการป้องกันการอาเจียนแบบล่าช้าต่ำกว่า คิดเป็นการป้องกันแบบสมบูรณ์ร้อยละ 76.4 สำหรับการป้องกันการคลื่นไส้แบบล่าช้า และร้อยละ 85.7 สำหรับการป้องกันการอาเจียนแบบล่าช้า ผู้ป่วยทนการรักษาได้ดี โดยไม่มีผลข้างเคียงรุนแรงจากยาโทรปิเซตรอน พบผู้ป่วยเพียง 4 ราย ที่มีอาการสะอึกซึ่งหายไปเองในตอนสิ้นสุดการให้ยา ยาโทรปิเซตรอนและยาเด็กซาเมธาโซนเป็นยาที่มีประสิทธิภาพและปลอดภัยในการป้องกันอาการคลื่นไส้อาเจียนจากยาเคมีบำบัดซีสพลาติน

คำสำคัญ : โทรปิเซตรอน, เด็กซาเมธาโซน, อาการคลื่นไส้อาเจียนจากยาซีสพลาติน

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จดหมายเหตุทางแพทย์ ฯ 2543; 83: 668–675

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