Evaluation of Safety and Efficacy of Transdermal Therapeutic System-Fentanyl in Adult Patients with Gynecological Cancer-Related Pain

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Abstract

Objectives : To assess the analgesic safety and efficacy of Transdermal Therapeutic System (TTS)-fentanyl in the treatment of chronic gynecological cancer-related pain.

Background : TTS-fentanyl is a Transdermal Therapeutic System, which contains a rate-limiting membrane that provides constant release of fentanyl. TTS-fentanyl can be properly used to control pain. Therefore, this trial was designed to establish the analgesic efficacy and safety of TTS-fentanyl in the treatment of chronic gynecological cancer-related pain.

Material and Method : Thirty patients were recruited into the study. This open study was comprised of two phases. Phase 1 : an oral morphine stabilization phase where eligible patients, who took other opioids and/or analgesic drugs, were entered into the stabilization phase and should be converted to oral morphine according to the conversion chart. The patients were then titrated to a stable oral morphine dose. Phase 2 : an open TTS-fentanyl treatment phase where the daily dose of oral morphine was switched to TTS-fentanyl according to the conversion chart. The efficacy parameters of pain score were assessed by visual analogue scale (VAS) and global assessments. The safety was evaluated by mornitoring the patient's clinical conditions and adverse events.

Results : TTS-fentanyl was generally well tolerated. Only one patient was dropped out from the study due to lacking enrollment in the stabilization phase. The most frequent adverse events were mild nausea or vomiting (46%) and constipation (33%). The median pain VAS during TTS-fentanyl treatment was decreased from 8 to 3 and global assessments at the end of the treatment were better than at the start of the treatment.

Conclusion : The results suggest that TTS-fentanyl is safe and effective in managing chronic gynecological cancer-related pain.

Key word : TTS-Fentanyl, Gynecological Cancer, Pain, Efficacy

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Fentanyl, a potent synthetic opioid, has been used for many years as an intravenous component of various general anesthetic regimens. Fentanyl-oxygen anesthesia has been called "stress-free anesthesia" because of the absence of deleterious cardiovascular effects(1).

The use of fentanyl for the control of chronic pain by conventional IM or IV bolus administration has been limited, because of its short duration of action. Some properties of the drug, however, suggest that it offers advantages over other analgesics if a simplified mode of parenteral administration is available. Compared with morphine, fentanyl exhibits; a higher clearance rate(1), greater penetration to the brain(2), a higher affinity for the mu opiate receptor (2), haemodynamic stability(3), and less histamine release(3,4). Fentanyl has been recently incorporated into a Transdermal Therapeutic System (TTS), which contains a rate-limiting membrane that provides constant release of the opioid. It is useful in managing chronic pain of moderate to severe intensity, since this transcutaneous system provides continuous controlled systemic delivery of fentanyl for up to 72 hours.

A major area for TTS-fentanyl use is in the management of terminal cancer-related pain. The prevalence of inadequate pain management has been estimated to occur in 60-80 per cent of cancer patients (5). The choice of drug and the method of administration has been cited as reasons for the inadequate analgesia(6). The swings in blood concentration caused by oral, IM, and IV bolus administered analgesics, may be accompanied by clinical responses fluctuating between ineffective analgesia and unwanted side effects (such as nausea or sedation)(7-9). Patient Controlled Analgesia (PCA) devices circumvent this problem and improve analgesia. However, the attendant costs, equipment, and personnel time requirements currently limit the usefulness of these devices(10,11).

TTS-fentanyl provides continuous opioid delivery without the need for special equipment. The noninvasive transdermal delivery route will not subject patients to the risks and discomfort inherent to the IV or SC route of drug administration. Also the simplicity of TTS-fentanyl allows freedom to maintain a relatively normal lifestyle, thereby enhancing the patients quality of life.

TTS-fentanyl has been shown to be safe and effective in the treatment of cancer pain, with a reduced incidence of some opioid related side effects(12-14). Cervical and ovarian cancer are the common cancers in Thai women. Most cases are in the advanced stage and suffering from cancer pain. TTS-Fentanyl may be properly used to control this pain. Therefore, this trial was designed to establish the analgesic efficacy and safety of TTS-fentanyl in the treatment of chronic gynecological cancer-related pain.

METHOD

Study design

This is a prospective, nonrandomized, open feasibility study of TTS-fentanyl in patients with gynecological cancer-related pain.

Inclusion criteria

1. Patients must have a histologically confirmed malignancy.
2. Patients must have moderate to severe pain caused by the presence of a malignant disease.
3. Patients must not require more than 404 mg of oral morphine daily or the equivalent with acceptable toxicity and adequate pain relief.
4. Patients must be able to give informed consent.
5. Patients must be able to communicate effectively with study personnel about the nature of their pain and be able to complete their daily treatment.

Exclusion criteria

1. Patients with a history of allergy to opioids.
2. Patients with a history of narcotic abuse prior to their diagnosis of cancer.
3. Patients with active skin disease that precludes application of the transdermal system.
4. Patients with a history of CO2 retention.
5. Patients with a serum bilirubin level > 2.0 mg/dl.
6. Patients with a serum creatinine level > 2.0 mg/dl.

Treatment design and assessment

This open study was comprised of two phases. Phase 1 : an oral morphine stabilization phase where eligible patients, who took other opioids and/or analgesic drugs, were entered into the stabilization phase and should be converted to oral morphine according to the conversion chart (Table 1). The patients where then titrated to a stable oral morphine dose. Phase 2 : an open TTS-fentanyl treatment phase where the daily dose of oral morphine was switched to the TTS-fentanyl (25, 50, 75 or 100 µg/h) administered as a transdermal path every 3 days. Patients were con-

Table 1. Opioid analgesic dose conversion to oral morphine[10].

Drug	Equianalgesic dose	
	IM*	Oral
Morphine	10	30 **
		60***
Hydromophone	1.5	7.5
Methadone	10	20
Oxycodone	15	30
Levorphanol	2	4
Oxymorphone	1	10
		(rectal)
Diamorphine	5	60
Pethidine	75	-
Codeine	130	200
Buprenorphine	0.3	0.8
		(sublingual)

* Based on single-dose studies in which an IM dose of each drug listed was compared with morphine to establish the relative potency. Oral doses are those recommended when changing from a parenteral to an oral route.

** The IM/oral potency ratio 1:3 for morphine is based on clinical experience in patients with chronic pain.

*** Assuming single or intermittent dosing.

verted from a daily dose of oral morphine to TTS-fentanyl according to the conversion ratio (Table 2). All patients were supplied with a morphine oral solution (2 mg/ml) for unlimited use to treat breakthrough pain. Patients recorded the use of supplement morphine oral solution for breakthrough pain. The efficacy parameters are pain score assessments by visual analogue scale (VAS) at day 1, 3, 6, 9, 12, 15, 18 and 21, and global assessments at day 1 and 21. Patients' vital signs, blood pressure and heart rate, were monitored throughout the study. The Karnofsky performance status was assessed at the beginning and the end of fentanyl treatment. Daily amount of morphine oral solution for breakthrough pain was also recorded. The safety was evaluated by monitoring the patient's clinical conditions and adverse events.

RESULTS

From September 2000 to May 2002, 30 patients were recruited into the trial. The mean age was 47 years old (range 30-64 years old). Twenty-nine patients completed the study. Only one patient dropped out from the study because he couldn't be included in the stabilzation phase. Twenty-nine patients were stabilized on morphine oral solution. After stabilization, they were switched to TTS-fentanyl. Patients' mean morphine requirements was 30.18 mg/day (range 20-80 mg/day). The total patients initial TTS-fentanyl dose requirements were 25 μg/h. There were significant differences in Karnofsky performance status during the treatment period. The Karnofsky score at the end of the treatment (90) was better than before the treatment (80). Mean morphine oral solution requirements for breakthrough pain were declined during the

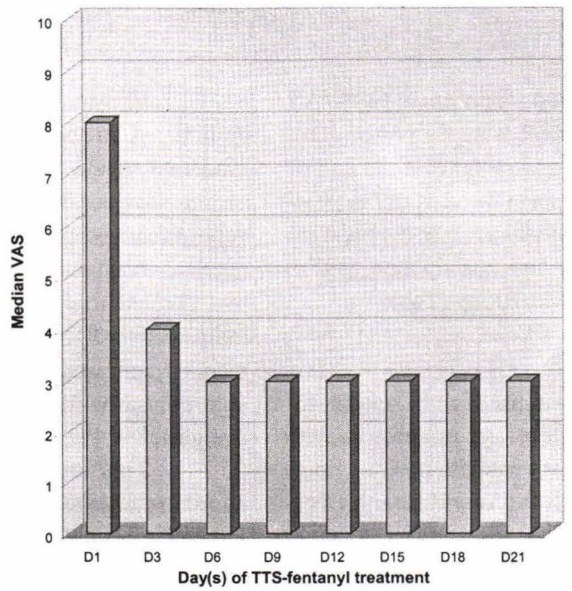

Fig. 1. Median pain visual analog scale during TTS-fentanyl.

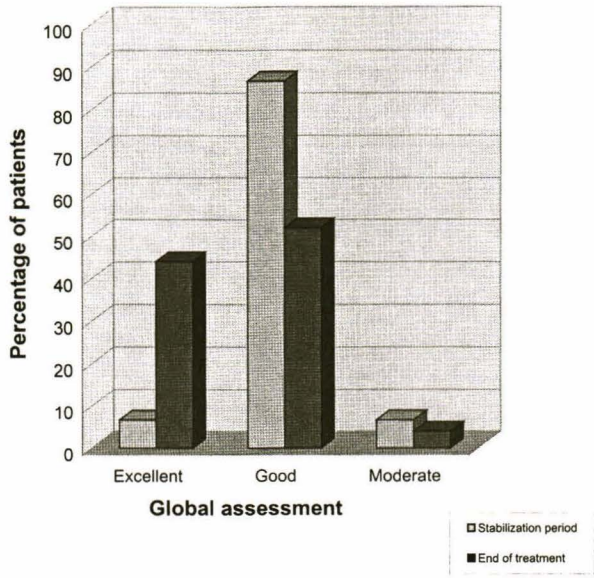

Fig. 2. Global assessment at the stabilization phase and the end of the treatment.

Table 2. Dose conversion from oral morphine to TTS-fentanyl.

Oral morphine (mg/24 h)	Initial TTS-fentanyl (μg/h)
< 134	25
135-224	50
225-314	75
315-404	100

Table 3. Adverse events during treatment.

Adverse events (grade 1 or 2)	Number of patients	%
Nausea/vomiting	14	46.6
Constipation	10	33.3
Anorexia	5	16.6
Itching	3	10.0
Dyspepsia & flatulence	1	3.3

TTS-fentanyl treatment period. The median pain VAS during TTS-fentanyl treatment were decreased from 8 to 3 (Fig. 1). The global assessments at the end of the treatment were better than at the start of the treatment (Fig. 2). The most frequent adverse events were nausea or vomiting (46%) and constipation (33%). There were no grade 3 and 4 toxicity (Table 3).

DISCUSSION

Opioids have been used with benefit for decades as potent analgesic drugs in subjects with acute and chronic pain. Treatment with potent opioids has been as the third step in the World Health Organization (WHO) analgesic ladder and is strongly encouraged in the management of cancer-related pain. However, these recommendations may also be applicable to chronic pain management[15].

TTS-fentanyl is designed to enable the use of fentanyl in the management of chronic pain of moderate severe intensity since this transcutaneous system provides continuous, controlled systemic delivery of fentanyl for up to 72 hours. In the latest of the regularly conducted safety updates, it was concluded that clinical trial data and pharmacovigilance data indicate that TTS-fentanyl, if prescribed as recommended and used under medical guidance, is a suitable treatment for chronic pain requiring an opioid analgesic[12-14].

This study has shown that TTS-fentanyl administered every 3 days is effective for the treatment of most patients with cancer -related pain. The initial report was performed by Miser[16] regarding the use of transdermal fentanyl for the pain control of five cancer patients and subsequent studies have

demonstrated the use of TTS-fentanyl for the management of severe cancer pain[17-20]. The present study corroborates the evidence of the usefulness of TTS-fentanyl for cancer-related pain management.

The interpretation of the safety data is undoubtedly complicated by the presence of serious underlying diseases. However, TTS-fentanyl appeared to be well tolerated by these severely ill patients. It was agreed by other studies that investigated cancer patients[13,17,21,22]. The incidence of serious and severe adverse events was related to exacerbations in the patients' underlying disease. The incidence of nausea, vomiting and constipation was similar in both the TTS-fentanyl treatment phase and the morphine stabilization phase.

The daily dose of rescue morphine for breakthrough pain declined during the TTS-fentanyl treatment phase. After 48 hours of the first application of TTS-fentanyl, the patients felt pain relief more than the previous morphine treatment. This result may support the fact that the dose of TTS-fentanyl was adequate for pain relief.

The results from this study demonstrate that TTS-fentanyl is useful for chronic gynecological cancer-related pain management. The use of TTS-fentanyl can improve the quality of life and reduce pain of the patients. The patients felt better than at the beginning of the treatment because TTS-fentanyl provides continuous controlled systemic delivery of fentanyl for pain relief up to 72 hours.

SUMMARY

The results suggest that TTS-fentanyl is safe and effective in the treatment of chronic gynecological cancer-related pain.

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การประเมินประสิทธิภาพและความปลอดภัยของการใช้แผ่นยาเฟนตานิลแก้ปวดชนิดปิดผิวหนังในการรักษาอาการปวดในผู้ป่วยหญิงที่เป็นมะเร็งอวัยวะสืบพันธุ์

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วัตถุประสงค์ : เพื่อประเมินประสิทธิภาพและความปลอดภัยของแผ่นยาเฟนตานิลแก้ปวดชนิดปิดผิวหนังในการรักษาอาการปวดเรื้อรังในผู้ป่วยหญิงที่เป็นโรคมะเร็งอวัยวะสืบพันธุ์

ภูมิหลังงานศึกษา : แผ่นยาเฟนตานิลแก้ปวดชนิดปิดผิวหนังเป็นระบบบริหารยาผ่านทางผิวหนัง ซึ่งประกอบด้วยเยื่อบาง ๆ ที่ควบคุมอัตราการปลดปล่อยของยาเฟนตานิลให้ออกมาด้วยอัตราคงที่ แผ่นยาเฟนตานิลแก้ปวดชนิดปิดผิวหนังมีคุณสมบัติควบคุมอาการปวด ดังนั้นในการศึกษาครั้งนี้จึงถูกออกแบบขึ้นเพื่อประเมินประสิทธิภาพและความปลอดภัยของแผ่นยาเฟนตานิลแก้ปวดชนิดปิดผิวหนังในการรักษาอาการปวดเรื้อรังในผู้ป่วยหญิงที่เกิดจากโรคมะเร็งอวัยวะสืบพันธุ์

วัสดุและวิธีการ : ผู้ป่วยจำนวน 30 รายที่เข้าร่วมในโครงการศึกษา การศึกษาในครั้งนี้ประกอบด้วย 2 ระยะ ระยะที่ 1 เป็นระยะปรับขนาดของยามอร์ฟีนให้เหมาะสมในผู้ป่วยในกรณีที่ผู้ป่วยเคยได้รับยากลุ่มมอร์ฟีนตัวอื่นและ/หรือยาแก้ปวดตัวอื่นโดยการปรับเปลี่ยนให้เป็นยามอร์ฟีนในรูปแบบยารับประทานโดยใช้แผนผังปรับเปลี่ยนขนาดยา ซึ่งผู้ป่วยจะได้รับการปรับขนาดยาเพื่อได้ขนาดมอร์ฟีนชนิดรับประทานที่เหมาะสม ระยะที่ 2 เป็นระยะที่ผู้ป่วยได้รับแผ่นยาเฟนตานิลแก้ปวดชนิดปิดผิวหนัง โดยขนาดของมอร์ฟีนที่ได้รับต่อวันในระยะที่ 1 ถูกเปลี่ยนเป็นแผ่นยาเฟนตานิลแก้ปวดชนิดปิดผิวหนัง โดยใช้แผนผังปรับเปลี่ยนขนาดยา การประเมินประสิทธิภาพของแผ่นยาแก้ปวดจะประเมินโดยใช้ระดับคะแนนความเจ็บปวด (Visual analogue scale) และการประเมินความรู้สึกของผู้ป่วยต่อการรักษา (Global assessments) ส่วนการประเมินด้านความปลอดภัยจะพิจารณาจากการเฝ้าดูอาการทางคลินิคของผู้ป่วย และอาการข้างเคียงที่เกิดขึ้น

ผลการศึกษา : ผู้ป่วยทนต่อแผ่นยาเฟนตานิลแก้ปวดชนิดปิดผิวหนังได้ดี มีเพียงผู้ป่วย 1 รายที่คัดออกจากการศึกษาเนื่องจากไม่ได้รับการปรับขนาดของยามอร์ฟีนให้เหมาะสม อาการข้างเคียงที่พบมากที่สุด คือคลื่นไส้ อาเจียนพบร้อยละ 46 และอาการท้องผูกพบร้อยละ 33 โดยค่ามัธยฐานของระดับคะแนนความปวดของระหว่างที่ได้รับการรักษาด้วยแผ่นยาเฟนตานิลแก้ปวดชนิดปิดผิวหนังลดลงจาก 8 เป็น 3 และเมื่อประเมินความรู้สึกของผู้ป่วยต่อการรักษาภายหลังจากสิ้นสุดการการใช้แผ่นยาเฟนตานิลแก้ปวดชนิดปิดผิวหนังมีค่าดีกว่าก่อนได้รับการรักษา

สรุป : ผลที่ได้จากการศึกษาพบว่าแผ่นยาเฟนตานิลแก้ปวดชนิดปิดผิวหนังมีประสิทธิภาพและปลอดภัยในการรักษาอาการปวดในผู้ป่วยหญิงที่เป็นโรคมะเร็งอวัยวะสืบพันธุ์เรื้อรัง

คำสำคัญ : แผ่นยาเฟนตานิลแก้ปวดชนิดปิดผิวหนัง, โรคมะเร็งอวัยวะสืบพันธุ์เรื้อรัง, อาการปวด, ประสิทธิภาพ

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