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Initial Dose Cascade of TTS Fentanyl with Proper Adjuvant Medications in Cancer Pain

According to the three step-ladder analgesics in patients with cancer pain, adjuvant drugs are required for pain relief according to the pain character and also to reduce side effects of opioids. Pain clinicians sometimes want to decide to jump directly from naive and mild opioid to transdermal therapeutic system (TTS) fentanyl with less side effects. We investigated the safety, efficacy, and satisfaction of the patients of TTS fentanyl converting from opioid-naive and mild-opioid with adjuvant drug medications in related to dose cascade of TTS fentanyl. Both opioid-naive (n=3) and opioid-using (n=34) patients started with TTS fentanyl in the lowest available delivery rate (25 μg/hr) with rescue medication. A numeric rating scale (NRS, from 0=no pain to 10=worst pain imaginable), satisfaction of the patients with the transdermal therapy and side effects were recorded everyday during 29 days. Average reductions of NRS scores were 1.79 and 2.77, and the mean doses were 35.14 and 44.12 μg/hr on the 15th and 29th day, respectively. Reported level of satisfaction with the transdermal patch and generalized pain management were 'completely satisfied' and 'satisfied'. Frequent side effects were nausea, vomiting, and constipation. In conclusion, initial application of TTS fentanyl with proper adjuvant medications is effective, safe, and well tolerated.

Key Words : *Adjuvants, Pharmaceutic; Analgesics; Drug Delivery Systems; Fentanyl*

Seong Wan Baik, Kyung Hoon Kim, Yong Chul Kim*, Sang Chul Lee*, Dong Ki Kim†, Jae Eun Jung‡

Department of Anesthesia and Pain Medicine, College of Medicine, Pusan National University, Busan; Department of Anesthesia and Pain Medicine*, College of Medicine, Seoul National University, Seoul; Department of Medical Statistics†, College of Medicine, Yonsei University, Seoul; Gastointestinal and Pain Medical Department‡, Janssen Korea Limited, Seoul, Korea

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Address for correspondence
Kyung Hoon Kim, M.D.
Assistant Professor, Department of Anesthesia and Pain Medicine, College of Medicine, Pusan National University, 1-10 Ami-dong, Seo-gu, Busan 602-739, Korea
Tel : +82.51-240-7391, Fax : +82.51-242-7466
E-mail : pain@pusan.ac.kr

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INTRODUCTION

To decide the proper administration of analgesic doses for the patients suffering from the cancer pain, pain clinicians are frequently skipping three-step analgesic ladder, as started in the WHO Guidelines of September 1986 on cancer pain management (1). A transdermal therapeutic system (TTS) of fentanyl was introduced in Korea in 1995. TTS fentanyl enables the noninvasive opioid administration in patients with dysphasia; patients who cannot tolerate oral therapy due to cancer-related side effects or due to side effects of the oral opioid itself (2). Now just like using the neural blockade or neural ablation at any steps, for the patients, who consider transdermal opioid as the best route to tolerate opioid-related side effects, transdermal fentanyl is another drug of choice to treat visceral and neuropathic pain from the cancer.

The purpose of the study was to investigate: 1) feasibility of direct conversion from naive and mild opioids to strong opioids fentanyl patch for the analgesia with concomitant administration of adjuvant drugs; 2) appropriate application intervals of TTS fentanyl for the effective analgesia; and 3) factors affecting patients' satisfaction and side effects on the clinical trial.

MATERIALS AND METHODS

The study was conducted in Pain Clinics of 2 University Hospitals in Korea for 29 days from June 2001 to June 2002. The study group consisted of 37 patients (14 men and 23 women; age range: 23-81 yr, mean±SD 51.7±12.0 yr) excluding 7 eliminated patients, with consultation from other departments due to uncontrolled cancer pain. The underlying primary tumor location listed in Table 1.

Inclusion criteria were: 1) patients who finished second outpatient department (OPD) visit and documented case sheets patients until Day 15; 2) histologically confirmed malignancy; 3) patients aged over 18 yr; 4) ability to communicate effectively with the study personnel regarding the nature of pain and quality of life of the patient; 5) adequate communication and cooperation with the family of the patient; 6) informed consent of the patient; and 7) intractable cancer pain treated with NSAIDs, mild opioids, and subcutaneous, intravenous, or intramuscular strong opioid administration intermittently <3 times/day for the rescue medication.

Exclusion criteria were: 1) patients already continuing medication with strong opioids for pain managements; 2) dying

Table 1. The underlying primary tumor location of participant patients

Tumor location	No. of patients (%)
Ovary/Cervix	10 (27)
Gastrointestinal tract	7 (19)
Head and Neck	5 (14)
Kidney/Bladder	4 (11)
Hepatobiliary	3 (8)
Lung	3 (8)
Other	5 (14)

patients or patients with impaired consciousness; 3) a history of CO_2-retention or other pulmonary problems; and 4) heptorenal failure (AST, ALT >100 U, BUN >10 mg/dL and Cr. >2.5 mg/dL).

The patients were hospitalized for the first 3 days of the study at least, and went through the baseline laboratory examination and medication for pain during the time. The investigators then had visited or phoned daily throughout the 29-day trial to evaluate the efficacy and safety of the TTS fentanyl. For the initial dose of transdermal fentanyl (Durogesic®, Janssen, Beerse, Belgium), the lowest delivery rate of 25 mg/hr was applied and the same application intervals had to be kept for 3 days according to the ordinary prescription method. On the first day of application, analgesics used before were continued until the initiation of effect of fentanyl patch.

Subcutaneous or intravenous morphine of 5 mg or suppository morphine of 10 mg was supplied as rescue medication when sufficient relief from pain was not adequate, because of either inadequate transdermal fentanyl dose or breakthrough pain. Through the trial, dose adjustment of fentanyl was determined by converting the mean daily rescue morphine dose, when needed on a regular basis over the 3 days preceding a patch renewal. In addition to the three step-ladder analgesics, adjuvant drugs including antidepressants, anticonvulsants, oral anesthetics, corticosteroids, myotonolytics, and neuroleptics were given to relieve from pain and to reduce opioid-related side effects. Depending on the rescue dose of morphine over 3 times in a day, we decided to increase the dose of fentanyl patch starting at next changing time.

The application sites were upper torso and upper arm, and had to be both nonirritated and nonirradiated. Rotation with each application site would be helpful to reduce skin reaction and variations in blood levels resulting from alterations in the skin under the previous patch.

At the beginning of the study, all patients had a physical examination and routine laboratory control. The investigators made baseline assessments of pain using a numeric rating scale (from 0=no pain to 10=worst pain imaginable) and overall satisfaction with application of fentanyl patch using verbal rating scale 1-5, with 1) not at all satisfied, 2) not satisfied, 3) fairly satisfied, 4) satisfied, and 5) completely satisfied. And the overall reported satisfaction of the patients for the pain control had used by the same scale as above.

Table 2. Medications used before and during the study

	During 2 wks prior to study (n=37)	Study days		
		1st day (n=37)	15th day (n=37)	29th day (n=34)
TTS fentanyl 25 μg/hr	-	37 (100)	24 (65)	18 (53)
50 μg/hr	-	-	11 (30)	8 (24)
75 μg/hr	-	-	2 (5)	6 (18)
100 μg/hr	-	-	-	2 (5)
Mean dose (μg/hr)	-	25.0	35.1	44.1
Acetaminophen	14 (38)	9 (24)	8 (22)	7 (21)
Acetyl salicylate	1 (3)	-	1 (3)	1 (3)
Codeine derivatives	27 (73)	23 (62)	1 (3)	-
Opioids*	8 (22)	6 (16)	-	-
NSAIDs	14 (38)	12 (32)	6 (16)	4 (12)
Tramadol	9 (24)	7 (20)	6 (16)	5 (15)
Antidepressants	-	11 (30)	13 (35)	11 (32)
Anticonvulsants	-	9 (24)	10 (27)	8 (24)
Minor tranquilizers	-	9 (24)	7 (19)	8 (24)
Antiemetics	-	8 (22)	6 (16)	5 (15)
Laxatives	-	5 (14)	7 (19)	7 (21)
Muscle relaxants	-	4 (11)	3 (8)	3 (9)
Antidiarrheals	-	1 (3)	-	-
Steroids	-	-	4 (11)	2 (6)

Data are numbers (%) of patients, TTS fentanyl=transdermal therapeutic system fentanyl.
*4 morphine (3 subcutaneous and 1 intravenous), 3 hycodone (oral), and 2 meperidine (intramuswlas). Four patients were prescribed two kinds of opioids simultaneously.

Patients or their family members at home were requested to write pain diary, which includes pain score, side effects, and rescue dose every day through the 29-day study. Patients had visited on the 15th and 29th days routinely. If patients had experienced some intolerable side effects such as nausea, vomiting, constipation, itching, respiratory depression, decreased mental status, or detachment from the skin due to sweating, anyone in the family was requested to contact us immediately and to be instructed by the treating doctors.

Statistical analysis was performed with χ^2-test and Student's t-test, as appropriate. The parametric data described as mean ±SD. Mantel-Haenszel chi-square test was used to evaluate the change of overall rate of satisfaction of the patients according to the TTS fentanyl dose increasing. Repeated measures ANOVA test was performed to compare daily changes of visual analogue scale between overall satisfaction and dissatisfaction group. Correlation analysis was performed to find out significant variables to influence the overall rate of satisfaction of the patients during treatment by using the logistic regression and the Fisher's exact test.

RESULTS

Among 44 patients, 7 patients were dropped out during the study due to intended removal of patch by patients themselves because of severe vomiting (n=2), hyperhidrosis (n=1), dizzi-

ness (n=1), severe abdominal pain (n=1), concomitant occurring paraplegia, urinary incontinence, and aphasia due to multiple cancer metastasis (n=1), and death from pulmonary embolism (n=1). After second OPD visit, 3 patients could not finish final report due to death (one from electrolyte imbalance on the 18th day and the other from severe dyspnea related pulmonary edema and acute renal failure on the 20th day), and self removal due to severe vomiting on the 25th day.

TTS fentanyl and various adjuvant medication administered during the study period and medications administered within 2 weeks before the study were presented on the Table 2. Morphine, codeine derivatives, hycodone, and meperidine were prescribed for the breakthrough pain as needed before and during the study period. Four patients were prescribed two kinds of opioids simultaneously. Various adjuvant drugs were noted on the first day of the study.

The numeric rating scale (NRS) pain scores of satisfaction group who were completely satisfied or satisfied with application of fentanyl patch were significantly lower than that of dissatisfactory group who were not at all satisfied or not satisfied. From the 18th day of the study, the two groups showed statistically significant difference on the pain scores (p=0.0024, Fig. 1).

Eighty-five and 88% of patients were satisfied with patch form opioid therapy and overall pain control with TTS fentanyl, respectively. The dosage of TTS fentanyl had influenced on the rate of satisfaction of the patients (p=0.003) (Table 3).

The univariate logistic regression analysis showed that pain,

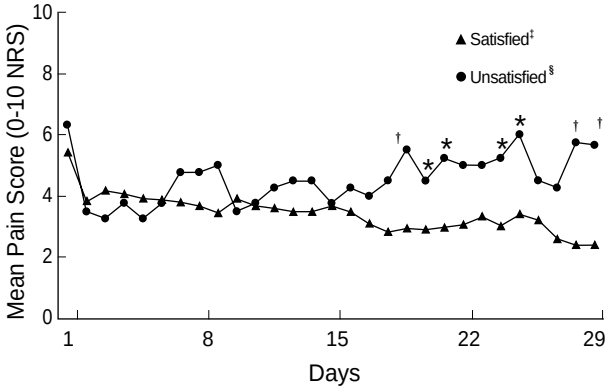

Fig. 1. Comparison of numeric rating scale between overall satisfaction and dissatisfaction group with application of TTS fentanyl.
TTS=transdermal therapeutic system.
Statistical analysis was done with Pooled or Satterhwaite method.
*p <0.05. †p <0.01. ‡Completely satisfied to satisfied and §fairly satisfied to not at all satisfied with overall pain management with TTS fentanyl, respectively.

Table 3. Assessment of overall satisfaction during the study

	Numeric rating scale*				
	1	2	3	4	5
Satisfaction with patch form opioid therapy	-	1 (3)	4 (12)	17 (50)	12 (35)
Overall satisfaction with pain control	-	1 (3)	3 (12)	16 (47)	14 (41)
Satisfaction according to the dose of TTS fentanyl†					
25 μg/hr	-	-	-	6 (18)	12
50 μg/hr	-	-	1 (3)	5 (15)	2 (6)
75 μg/hr	-	1 (3)	1 (3)	4 (12)	-
100 μg/hr	-	-	1 (3)	1 (3)	-

Data are numbers (%) of patients.
TTS fentanyl = transdermal therapeutic system fentanyl.
*1=not at all satisfied; 2=not satisfied; 3=fairly satisfied; 4=satisfied; 5=completely satisfied. †p-value=0.003 from the Mantel-Haenszel chi-square test.

Table 4. Potential predictors of overall satisfaction to the TTS fentanyl by logistic regression (LR) analysis

Variables	Overall Satisfaction		Univariate LR		Multivariate LR	
	Satisfied‡ (n=30)	Unsatisfied§ (n=4)	OR	95% CI	OR	95% CI
Male/Female	11/19	2/2	1.73	(0.21-14.05)	NS	NS
Pain (0-4/5-10)	25/5	1/3	15.00*	(1.28-175.30)	NS	NS
TTS fentanyl dosage (25-50/75-100 μg/hr)	25/5	1/3	15.00*	(1.28-175.30)	NS	NS
Satisfaction to patch form opioid therapy	28/2	1/3	42.00†	(2.88-621.29)	42.00†	(2.88-621.29)
Rescue medication‖ (Y/N)	5/25	3/1	15.00*	(1.28-175.30)	NS	NS
Defecation						
No./wk (≥3/<3)	29/1	4/0	-	-	-	-
Hardness (Diarrhea-normal/Constipation)	19/11	2/2	1.73	(0.21-14.05)	-	-
Difficulty on defecation (Y/N)	13/17	3/1	3.92	(0.37-42.19)	-	-
Use of laxatives¶ (Y/N)	10/20	2/2	2.00	(0.244-16.362)	-	-
Skin reaction** (Y/N)	2/28	0/4	-	-	-	-

Data are number of patients. p values and odds ratios (OR) are given to the variables that were experienced by ≥5% of either group. These values cannot be directly computed from the information provided. 95% CI=95% confidence interval, NS=not significant, Y=yes, N=no.
*p<0.05. †p<0.01. ‡Completely satisfied and satisfied and §fairly satisfied to not at all satisfied with overall pain management with TTS fentanyl. ‖Morphine (intravenous, rectal suppository, oral, subcutaneous). ¶MgO, glycerine enema, and bisacodyl, etc. **Erythema, edema, and itching.

dosage of TTS fentanyl, satisfaction to patch form opioid therapy, and rescue medication were significantly related to the overall satisfaction with TTS fentanyl therapy. However, satisfaction with patch form opioid therapy only showed closely related on the multivariate regression analysis (Table 4).

During the study, frequent complaints associated with application of fentanyl patch were nausea (n=14), vomiting (n=11) and constipation (n=6). And the other side effects were itching on the application sites (n=2), abdominal pain (n=2), loss of appetite, urinary retention (n=1), dizziness (n=2), sleepiness (n=2), general fatigue (n=1), and decreased consciousness (n=1). Among the side effects, factors affecting to the satisfaction of the patients were nausea, vomiting, and constipation. Such side effects did not show significant correlation with the overall satisfaction with TTS fentanyl therapy.

DISCUSSION

There are three major pharmacokinetic features of transdermal fentanyl system. The first is a lag period after the first dose of fentanyl before blood concentrations approach therapeutic levels. The actual minimal effective concentration may change depending on the intensity of the pain, the duration of pain, and the extent of previous opioid therapy. This lag period can vary from 1 hr to longer than 30 hr, with a mean value of about 13 hr (3). Therefore bridging or supplemental immediate-release analgesia must be administered for first 13 hr, depending on the amount and efficacy of the current analgesic regimen. A similar situation is likely to arise, if the transdermal fentanyl dose is increased because of inadequate analgesia. The abstinence/withdrawal syndrome may occur in the presence or absence of adequate analgesia. We used the same previous analgesic regimen on the first application of patch for 1 day except some changes of adjuvant medications. Patients had usually received the adequate analgesia around 12 to 24 hr with feasibility of direct conversion from naïve and mild opioids to strong opioids fentanyl patch for the analgesia with concomitant administration of adjuvant drugs, if needed. If possible, it is more reasonable to apply after dinner to consider this lag period. For the initial dose titration, these options are recommended: 1) patient-controlled analgesia with fentanyl to establish an hourly fentanyl demand rate for effective analgesia (4); 2) starting with the lowest possible transdermal fentanyl dose (25 μg/hr) and titration according to the response of the patient (5); or 3) using conversion tables that suggest a transdermal fentanyl dose taking the current analgesic regimen (in morphine equivalents) into consideration (6, 7). According to equianalgesic dose of opioid agonist analgesics, codeine 60 mg/day is similar to fentanyl patch 5 μg/hr. Therefore, if we use codeine 300 mg/day, the effect is the equianalgesic dose of fentanyl patch 25 μg/hr respectively.

Second, blood concentrations continue to rise and approach steady by the second dose, or possibly earlier with a 3-day dosing interval (4). In our study, we could find some differences of NRS scores among the first, second, and third days of application of patch. The mean NRS score of the second day (3.49 ±0.35) was significantly lower than that of the first day (3.78 ±0.71, p=0.0005), however, not significantly different from that of the third day (3.51 ±0.40, p=0.0967). So we have to consider the appropriate application intervals of TTS fentanyl for the effective analgesia with some patients. Steady-state blood fentanyl concentrations achieved with a given dose can vary among patients by factors such as increased skin hydration, skin damage by disease, chemicals and sun exposure, increased activity of sweat glands, increased perfusion during exercise, and elevated cutaneous temperature (3).

Third, once the systems are removed, the blood fentanyl concentration does not immediately fall at a rate predicted from intravenous fentanyl pharmacokinetics (3, 5). Thus both analgesia and any side effects that may be present will decline gradually after patch removal.

The delay in establishing effective blood fentanyl concentrations occurs because of the time taken to create a cutaneous depot of fentanyl in the skin covered by the system. Therefore, the system release fentanyl at a constant rate for up to 3 days. When the system is removed, a depot of fentanyl remains in the stratum corneum that was covered by the patch about 10% of the original dose, and absorption continues from this site thereby maintaining blood fentanyl concentrations.

The dose has varied by increasing or decreasing the number and/or size of the applied systems from the four available sizes, and there is dose proportionality with blood fentanyl concentrations according to linear pharmacokinetics (4). If we are unable to get the dose of fentanyl patch, 50, 75, and 100 μg/hr and have to use the fentanyl patch with combination of 25 μg/hr only, it can be administrated with over- or under-treatment.

Age seems to have an influence on transdermal fentanyl pharmacokinetics, specifically in older patients. Elderly patients usually required early patch removal owing to adverse effects, compared with younger patients. In contrast, the pharmacokinetics of transdermal fentanyl in children with cancer pain appears to be similar, but perhaps less variable, than in adults (8). In our study patients, aged from 25 to 81 yr old, age did not seem to have less influence on application of fentanyl pharmacokinetics.

The problem of the adherence or dehiscence of TTS fentanyl in patients with excessive sweating, in whom there is a possible reduction in effective surface area for absorption because droplets of fluid form under the patch (9). Among the 7 dropouts, one patient could not attach the patch because of excessive sweating.

All of the studies about the rate of satisfaction of the patients with TTS fentanyl, compared with slow-release morphine (SRM) formulations, indicated significantly greater satisfaction and willingness to continue the therapy (5, 9, 10). And a marked sex difference in satisfaction was shown in one study in which male but not female patients, reported a preference

for TTS fentanyl (10).

We, however, had studied about satisfying factors with fentanyl patch application itself and the reported satisfaction by the patients with dose escalation of fentanyl. Application of fentanyl patch to the patients suffering from cancer pain was noninvasive and easy to learn to apply, to give them relatively long-term analgesia. So, most of the patients preferred patch application to other method of drug delivery systems, including intravenous and epidural analgesia. And 23 patients among the 44 participants, including all dropouts suffered from the opioid-related side effects; nausea (n=14), vomiting (n=11), constipation (n=6) and so forth. These three side effects were major complaints and became major unsatisfied factors among the participants. In some other ways, we can presume the symptoms to be cancer-related problems. The group who needed lower dose of fentanyl, however, seemed to have higher rate of satisfaction for the pain management than the group who required higher dose of fentanyl. Therefore, the less opioids can give them the more satisfaction without side effects. The best way to reduce the dose of opioids is to find the characteristics and origins of pain. We tried to administer proper adjuvant medication as possible (Table 2). Patients with nausea and vomiting were treated with metoclopramide, ondansetron, scopolamine, and steroids. And patients with constipation were treated with MgO, senna, lactulose, bisacodyl, and glycerin enema.

Most patients with advanced cancer develop diverse symptoms that can limit the efficacy of pain treatment and undermine their quality of life. According to Meuser et al. (11), controllable symptoms were anorexia, impaired activity, confusion, change of mood, insomnia, constipation, dyspepsia, dyspnea, coughing, dysphasia, and urinary symptoms. But during the combination treatment with opioid and adjuvant drugs, sedation, other neuropsychiatric symptoms and dry mouth were significantly increased. Coma, vertigo, diarrhea, nausea, vomiting, intestinal obstruction, erythema, pruritus, and sweating, however, remained unchanged. The symptoms as being most frequently caused by the analgesic regimen were only constipation, erythema, and dry mouth. Nevertheless, general, neuropsychiatric, and gastrointestinal symptoms occurred during a major part of treatment time, and proper relief from pain was inadequate in 14% of patients. Cancer pain management has to be embedded in a frame of palliative care, taking all the possibilities of symptom management into consideration.

We conclude that initial application of TTS fentanyl combined with proper adjuvant medication is effective, safe, and well tolerated by most patients with cancer pain. And to manage nausea, vomiting and constipation induced by TTS fentanyl will increase rate of the satisfaction of the patients during initial dose cascade of fentanyl. With some patients, we have to consider the appropriate application intervals of TTS fentanyl for the effective analgesia.

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