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Case Report

Three-cycle fentanyl patch system contributes to stable control of plasma fentanyl concentration in gynecologic cancer pain patients

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Abstract

Objective: Pain affects many cancer patients in advancing stages, lowering the level of their quality of life. Morphine has long been the "gold standard" for the treatment of cancer pain; however, its side effects, particularly sedation and cognitive impairment at high doses, have encouraged the use of "opioid rotation". The transdermal fentanyl patch has advantages over oral morphine, with reduced side effects and increased convenience in practical usage. The side effects were reduced in patients who changed to the fentanyl patch, but rescue analgesia was often needed because of the decrease of fentanyl release from the patch, especially on patch replacement day. To maintain a stable fentanyl plasma level before patch replacement, we have established a three-cycle fentanyl patch system and reported that it provided appropriate pain control. The objective of this study was to investigate the individual variability of plasma fentanyl concentration in a three-cycle fentanyl patch system.
Case Report: The gynecologic cancer patients were treated using the three-cycle fentanyl patch system. Blood samples were taken from the patients and plasma fentanyl concentration was analyzed. A stable plasma fentanyl level was observed, and good pain control was achieved in each patient using the three-cycle fentanyl patch system. A stable plasma fentanyl level was maintained the day before the conventional patch replacement day.
Discussion: The three-cycle fentanyl patch system provided a stable plasma fentanyl concentration and excellent pain relief and should be considered for pain control in cancer patients.

Keywords: Cancer pain; Opioid rotation; Opioid therapy; Pain control; Transdermal fentanyl

Introduction

Fentanyl, a potent μ-selective opioid receptor agonist, is effective for the management of severe cancer pain. In patients with intolerable pain, transfer to a transdermal fentanyl patch offers an efficient and safe long-term analgesic option [1]. The transdermal fentanyl patch was launched in Japan in March 2002 and has enabled opioid rotation. Fentanyl has been incorporated into a transdermal therapeutic system containing a rate-limiting membrane that provides constant release of the opioid from a reservoir. Plasma fentanyl concentrations are barely detectable for about 2 hours after patch placement [2]. Eight to 12 hours after patch placement, plasma fentanyl concentration is approximately equal to that achieved with an equivalent intravenous dose of fentanyl [3]; therefore, it is recommended that the patches should be changed every 72 hours. However, on the third day, before patch replacement, pain control deteriorates because of decreased fentanyl release from the patch. It was reported that patients complained of severe pain on the replacement day in about one quarter of cases [4].

To maintain constant plasma level of fentanyl, we have established a three-cycle fentanyl patch system. Three patches were provided and were applied singly over 3 consecutive days at 24-hour intervals, and replaced every 72 hours. One-third of

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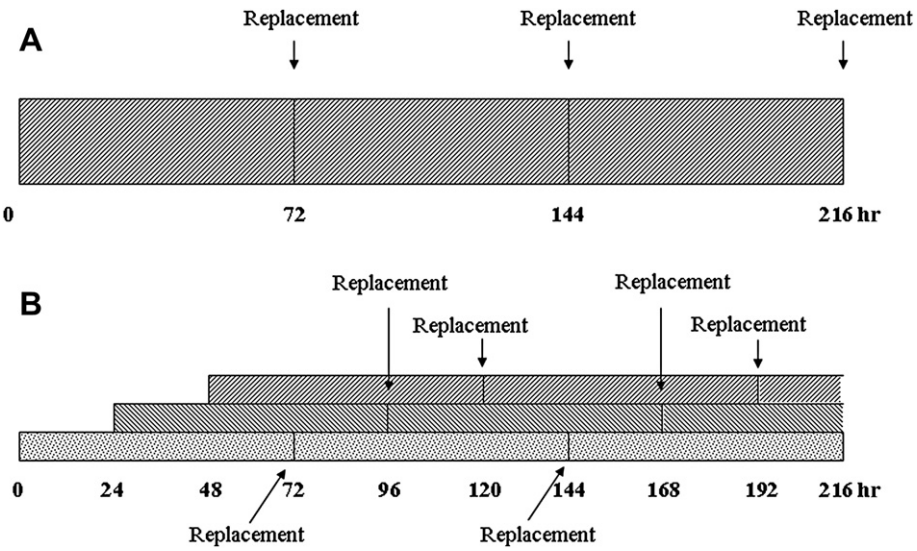

Fig. 1. Fentanyl patch application. (A) Conventional usage as recommended by the manufacturer. The fentanyl patch is designed to release fentanyl at a constant rate for up to 72 hr. Application is recommended for every 72 hr. (B) Three-cycle fentanyl patch system. Three patches were provided, applied singly over 3 consecutive days at 24-hr intervals, and replaced every 72 hr. One-third of the patches was replaced every day to maintain a plasma level of fentanyl.

the patches was therefore replaced every day to maintain a stable serum level of fentanyl (Fig. 1). We have reported that this system markedly improved cancer pain control [5].

In this study, we investigated plasma fentanyl levels in gynecologic cancer patients using the three-cycle fentanyl patch system. Stable plasma fentanyl concentration was shown throughout the three-cycle fentanyl system application. Stable control of the plasma fentanyl level was observed on the third day corresponding to the day before patch replacement in conventional usage. The three-cycle fentanyl patch system provided a stable plasma fentanyl level and excellent pain control.

Patients and treatment

Between May 2007 and May 2008, five patients with cancer-related pain who were hospitalized in Kansai Medical University Hospital were treated using the three-cycle fentanyl patch system. Three patches were provided and were applied singly over 3 consecutive days at 24-hour intervals, and replaced every 72 hours. One-third of the patches was therefore replaced every day to maintain a stable plasma level of fentanyl (Fig. 1). Three of the five patients were used for plasma fentanyl level analysis, and 15 plasma samples were analyzed. All patients were fully informed about the procedure and the purpose of this experiment, and gave written consent. All protocols were approved by the local Human Investigation Committee.

Blood collection

Blood samples were collected three times every consecutive 3 days 2 hours before fentanyl patch replacement: Day I corresponds to the conventional fentanyl patch replacement day, Day II is the day after Day I, and Day III is the day after Day II, corresponding to the day before fentanyl patch replacement in conventional usage. Blood samples were collected in heparinized glass tubes. Blood samples were centrifuged (2,000*g* for 10 minutes) and then the plasma was transferred to polypropylene tubes and stored at −80°C until analysis.

Plasma fentanyl concentration analysis

To 200 μL plasma, 50 μL of methanol, 50 μL of the internal standard solution (50 ng/mL methanol), 0.3 mL of water, and 1 mL of 0.1 mol/L sodium hydroxide were added and vortexed. A 3.5 mL mixture of heptan and isoamylalcohol (95:5,v/v) was added and the samples were shaken for 10 minutes. The organic phase of samples was extracted followed by centrifugation. Then, 4 mL of 0.05 mol/L sulfuric acid was added, the samples were shaken and centrifuged, and then the organic phase was carried out. Then, 0.15 mL of 28% ammonium hydroxide and a 2.5 mL mixture of heptan and isoamylalcohol (95:5,v/v) were added to the liquid phase and the samples were shaken for 10 minutes. The organic phase of samples was extracted, followed by centrifugation, and evaporated at 50°C with a nitrogen evaporator. The residue was reconstituted in 50 μL of methanol and 2 μL was injected into the Gas Chromatograph/Mass Spectrometer system.

Statistics

Statistical analysis was performed using Stat View software (SAS Institute Japan Ltd, Tokyo, Japan). The Friedman test was used to compare the dispersion of plasma fentanyl concentration on 3 consecutive days in the three-cycle fentanyl patch system. The *p* values below 0.05 were considered to indicate statistical significance.

Case Reports

Five patients were treated with the three-cycle fentanyl patch system in this study. This system brought an effective

and stable pain relief to all five patients. However, in two of them, enough blood samples were not obtained for plasma fentanyl concentration analysis. We presented three cases and stable plasma fentanyl concentration was shown throughout the three-cycle fentanyl system application.

Case 1

A 56-year-old woman with stage IV ovarian clear cell carcinoma diagnosed by an exploratory laparotomy with intraperitoneal chemotherapy (CDDP was medicated intraperitoneally) was given 6 cycles of chemotherapy (paclitaxel and carboplatin). Twelve cycles of weekly paclitaxel chemotherapy followed; however, a few months later she showed symptoms of peritonitis carcinomatosa because of recurrent tumor. She suffered severe pain and a fentanyl patch treatment was started. The fentanyl patch treatment relieved her pain with a dose up to 125 mcg/hr, and her visual analog scale (VAS) pain score decreased from 5 to 1 following its application, however, she complained of severe pain on the patch replacement day. Therefore, a three-cycle fentanyl patch system was started, and brought an effective pain relief and kept stable VAS pain score (Fig. 2A). Fentanyl 125 mcg/hr brought about effective pain relief without nausea; 25 mcg/hr patch was applied on the first day, 50 mcg/hr patch the next day, and 50 mcg/hr patch on the third day (Fig. 2B). In this figure, Day I was the day corresponding to the patch replacement day in conventional usage. On Day II, one of the fentanyl patches was replaced during the three-cycle fentanyl patch system application; however, it was not replaced in conventional usage. Day III was the patch replacement day in the three-cycle fentanyl patch system and before patch replacement in conventional usage. The plasma concentration of fentanyl was analyzed and revealed a stable level throughout the three-cycle fentanyl patch system application (Case 1 in Fig. 3). The patient was mentally alert, and could eat (VAS score remained $\leq$2) during her final 5 months with the high-dose three-cycle fentanyl patch system.

Case 2

A 45-year-old woman diagnosed with uterine cervical cancer (clinical stage IIIb, squamous cell carcinoma) was treated with primary radiation therapy (total 65 Gy) followed by four cycles of

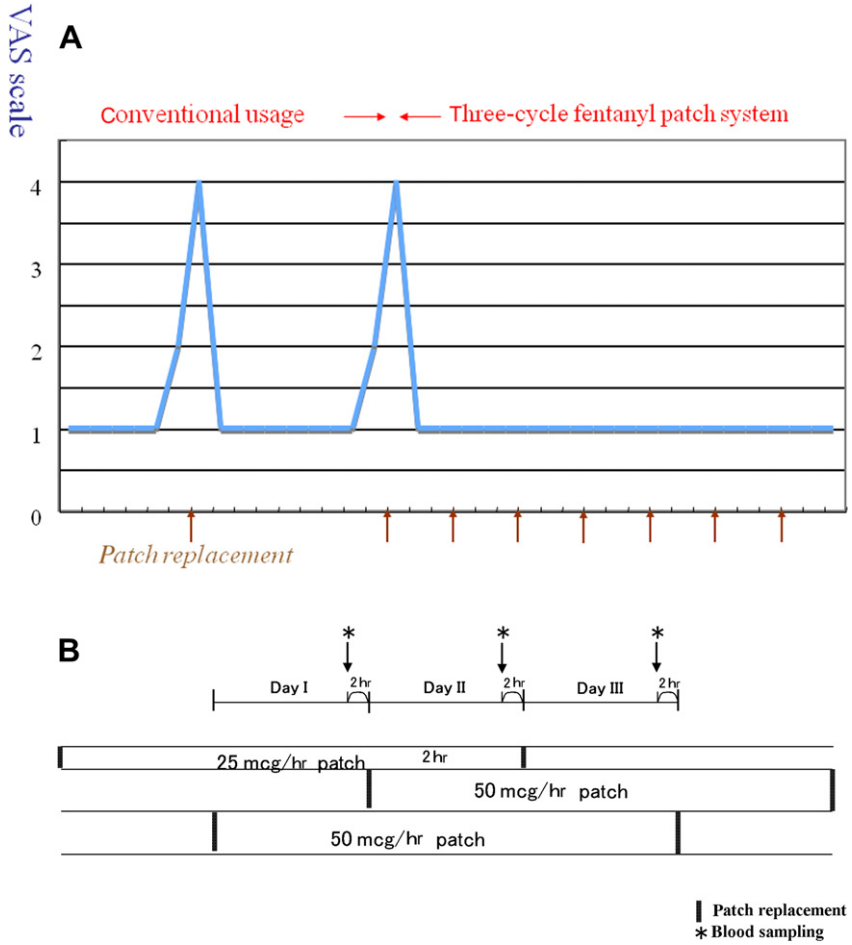

Fig. 2. Three-cycle fentanyl patch system of Case 1. (A) VAS pain score deteriorated on the third day before patch replacement in the conventional usage. The three-cycle fentanyl patch system provided an excellent pain relief and VAS pain score was stabilized. (B) A 125 mcg/hr fentanyl brought pain relief and plasma fentanyl level was analyzed on 3 consecutive days. VAS = visual analog scale.

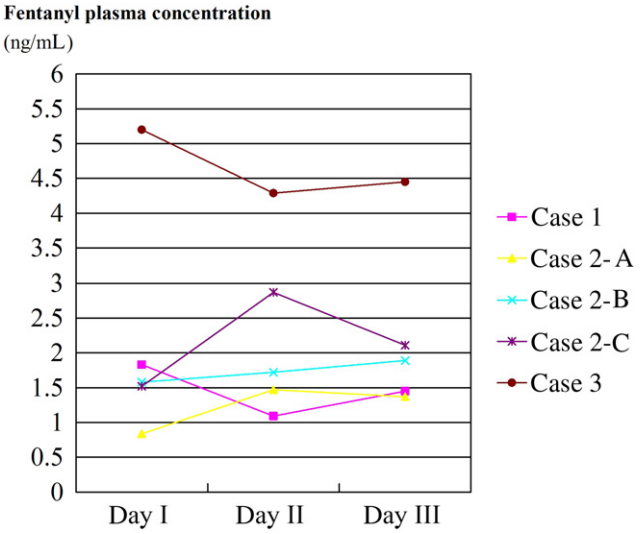

Fig. 3. Plasma fentanyl level during application of the three-cycle fentanyl patch system. The plasma fentanyl concentration of three cases was analyzed.

chemotherapy (paclitaxel and carboplatin) with thermotherapy. Several months later, recurrent tumor invaded her ureter and rectum, causing hydronephrosis and renal failure. A nephrostomy was established and a three-cycle fentanyl patch system was applied to control her severe pain because nonsteroidal anti-inflammatory drugs were unsuccessful. Her VAS score decreased from 5 to 1 following the three-cycle fentanyl patch system application. Plasma concentration of fentanyl was studied at 75 mcg/hr fentanyl dose (Case 2-A in Fig. 3); one of the 25 mcg/hr patches was replaced every day (Fig. 4A). Two months later, her VAS score increased to 5 again and the dose of fentanyl was increased to 125 mcg/hr (Fig. 4B), bringing good pain relief (VAS score 1), and the plasma concentration of fentanyl was studied (Case 2-B in Fig. 3). The dose of fentanyl was finally increased to 150 mcg/hr with good pain control (Fig. 4C) and plasma concentration of fentanyl was stable (Case 2-C in Fig. 3). She was mentally alert, and could eat during her final 5 months with the high-dose three-cycle fentanyl patch system.

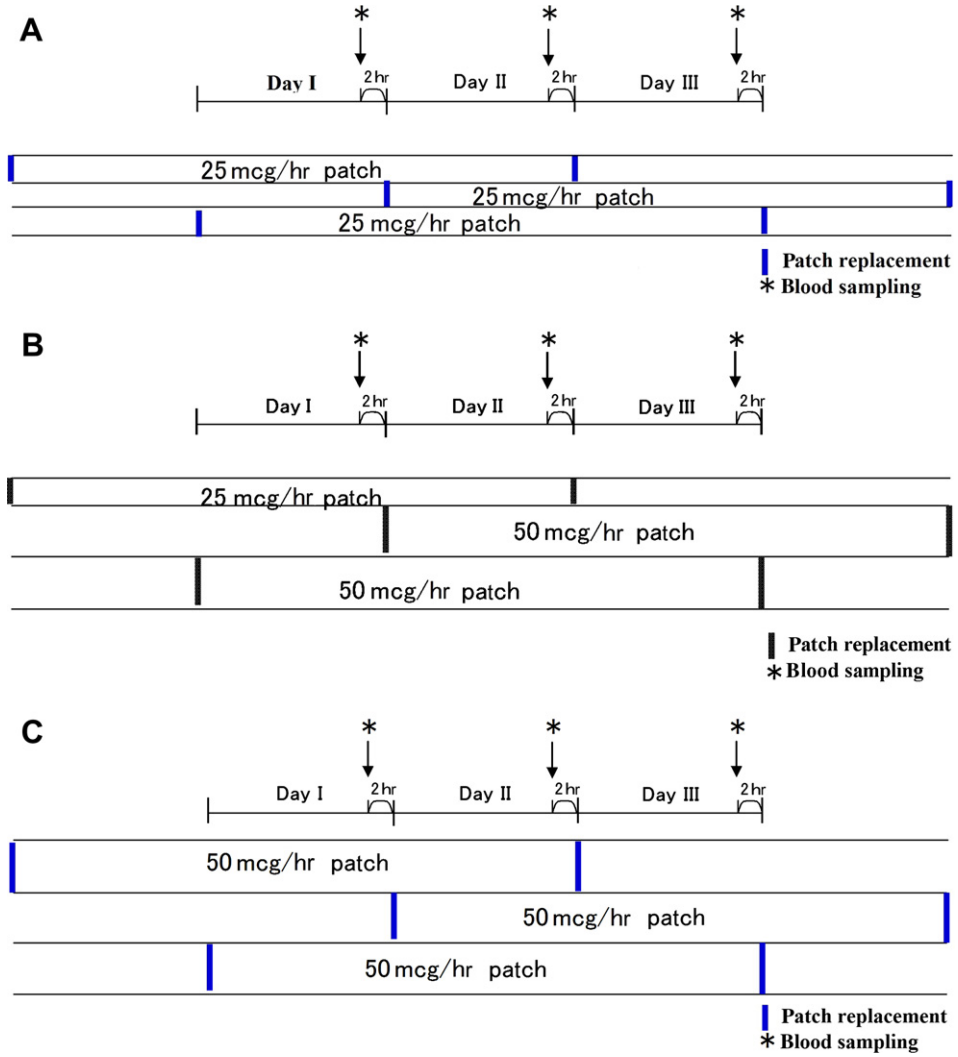

Fig. 4. Three-cycle fentanyl patch system of Case 2. (A) A 75 mcg/hr fentanyl brought pain relief and plasma fentanyl level was analyzed on 3 consecutive days. (B) A 125 mcg/hr fentanyl brought pain relief and plasma fentanyl level was analyzed on 3 consecutive days. (C) A 150 mcg/hr fentanyl brought pain relief and plasma fentanyl level was analyzed on 3 consecutive days.

Case 3

A 63-year-old woman had ovarian cancer stage IIIc endometrial adenocarcinoma of ovary diagnosed by total hysterectomy, bilateral salpingo-oophorectomy, and partial omentectomy. Thirty cycles of chemotherapy (paclitaxel and carboplatin) were given in the following 6 years; however, she showed symptoms of peritonitis carcinomatosa because of recurrent tumor and suffered severe pain, and a three-cycle fentanyl patch system was started. Fentanyl 75 mcg/hr brought about effective pain relief without nausea, and her VAS score decreased from 4 to 1 following this system application (Fig. 5). The plasma concentration of fentanyl was studied and was stable (Case 3 in Fig. 3). The pain was relieved (VAS score remained $\leq$2) and she was mentally alert, and could eat with the high-dose three-cycle fentanyl patch system.

Discussion

The transdermal patch was designed to release fentanyl at a constant rate for up to 72 hours. The amount of drug released is proportional to the surface area of the patch, and four different sizes are currently available with release rates of 25, 50, 75 and 100 mcg/hr. Fentanyl is a synthetic opioid with short-acting analgesic activity. The fentanyl patch is very useful for cancer pain control, however, pain control deteriorates because of decreased fentanyl release from the patch on the third day before patch replacement. It was reported that patients complained of severe pain on the replacement day in about one quarter of cases [4]. This tendency was more significant as the fentanyl dose increased. It was reported that plasma fentanyl levels of patches depend on the dose, and a positive correlation between plasma fentanyl concentrations and the fentanyl patch dose was confirmed [5–9]. Strong pain requires a dose of fentanyl. The decrease of fentanyl is augmented on patch replacement day as the fentanyl dosage increases and could cause more severe pain before patch replacement in conventional usage. To obtain a constant plasma level of fentanyl, we have established a three-cycle fentanyl patch system; three patches were provided and applied singly over 3 consecutive days at 24-hour intervals, and replaced every 72 hours. One of the patches was therefore replaced every day to obtain stable plasma levels of fentanyl. We have reported three cases in which this system markedly improved the control of cancer pain [5]. In this report, the fentanyl plasma level during this system was studied and a stable plasma fentanyl concentration was shown on Day III corresponding to before patch replacement (Fig. 3). We observed no significant difference in fentanyl plasma levels between Day I, II, and III in five sets of analysis during the three-cycle fentanyl patch system application (Friedman test, $p = 0.78$). This study confirmed that stable plasma fentanyl concentration was maintained on the third day, corresponding to before conventional patch replacement.

The fentanyl patch was reported to have fewer adverse events than oral morphine treatment [6–10]. The most frequently mentioned adverse events were reportedly nausea, vomiting, and constipation. Clinical data show that constipation occurs less frequently with transdermal fentanyl than with oral morphine therapy [9,10]. One reason for this may be the difference between the concentration required to achieve analgesia and the concentration required to elicit a reduction in intestinal activity. In addition, it was reported that fentanyl had a high affinity mu_1 site of opioid receptors, and the affinity of fentanyl for mu_2 receptors was lower than oral morphine [11]. The mu_2 receptors mediate respiratory depression, physical dependence, and inhibition of gastrointestinal motility. Respiratory depression is the most serious adverse event related to opioids. In this study, we noticed no respiratory depression. This shows that fentanyl patches can be used safely even in an opioid-naive setting in patients with no history of CO_2 retention. This finding is consistent with previous studies [12].

Fentanyl patches should only be used in patients who are already receiving opioid therapy according to Japanese medical insurance and medication guide; therefore, we had to use other opioids (excluded fentanyl patches) before the first application of the fentanyl patch. The rise of the fentanyl plasma level at the first patch application is gradual, and patients cannot absorb excess opioid doses. [4–8] It is more useful to apply fentanyl patches as the first opioid and this could achieve excellent pain control with the initial fentanyl application. We think that fentanyl patches could be used for the initial opioid application when used in nonsteroidal anti-inflammatory drug-tolerant patients.

Different from gastric cancer, gynecologic cancer patients could eat and drink until the terminal stage in many cases. The

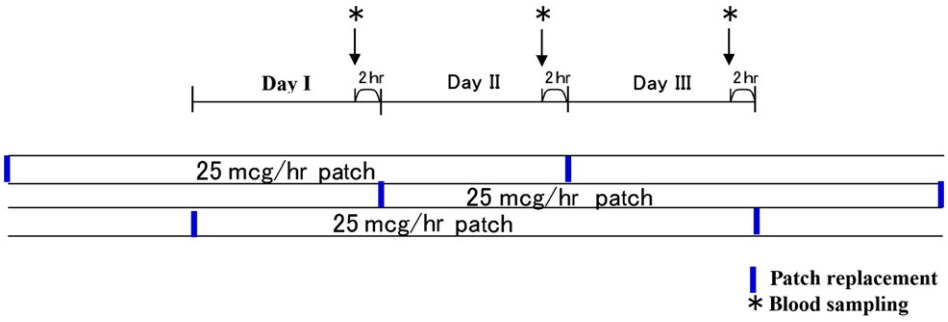

Fig. 5. Three-cycle fentanyl patch system of Case 3. A 75 mcg/hr fentanyl brought pain relief and plasma fentanyl level was analyzed on 3 consecutive days.

three-cycle fentanyl patch system therefore hardly limits patients' behavior. During application of the three-cycle fentanyl patch system, many patients could eat, drink, and stay overnight at home until the final stage. All patients described the convenience of patch use as excellent. The administration method of this system is extremely easy compared with a continuous drip, and home recuperation could be possible because patients could replace the patches at home after training. This system can provide stable pain control and allows freedom from injections, thereby enhancing the patient's quality of life. The three-cycle fentanyl patch system is effective and safe for the management of cancer-related pain and should be considered for pain relief in cancer patients.

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