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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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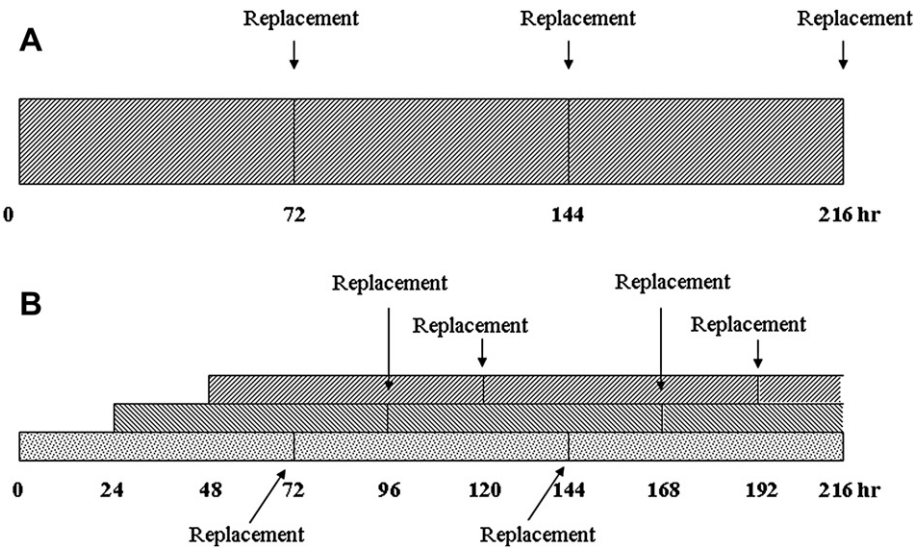

Fig. 1. Fentanyl patch application. (A) Conventional usage as recommended by the manufacturer. The fentanyl patch is designed to release fentanyl at a constant rate for up to 72 hr. Application is recommended for every 72 hr. (B) Three-cycle fentanyl patch system. Three patches were provided, applied 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