**Regular Article**

**Risk Factors for Poor Pain Control after Opioid Switching from Oxycodone Tablet to Fentanyl Patch**

Norimichi Morikawa,*a Yoko Kasahara,b Yuko Takahashi,a Kyoko Nishikura,a and Masayuki Nishihara*a

*a Department of Pharmacy, Mazda Hospital of Mazda Motor Corporation; 2–15 Aosakiminami, Fuchu-cho, Aki-gun, Hiroshima 735–8585, Japan; and b Department of Pharmacy, Hiroshima Prefectural Hospital; 1–5–54 Ujinakanda, Minami-ku, Hiroshima 734–8530, Japan.

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Pain control becomes poor in some cases after opioid switching from oxycodone tablet (OXC) to fentanyl patch (FP). However, fewer studies on risk factors have been reported. In this study, we surveyed the states of pain control (PC) and opioid administration, patient background, laboratory test values, and concomitant drugs retrospectively in 86 patients switching from OXC to FP between June 2010 and April 2018 in Mazda Hospital and Hiroshima Prefectural Hospital. The subjects were divided into 2 groups based on the median number of days to the initial dose increase after switching to FP. Between the early (<7.5d) and late (≥7.5d) increase groups, a significant difference was noted in the presence or absence of liver metastasis (LM), concomitant drugs with a high protein binding rate (CDHPBR), and the state of PC before and after switching to FP (p < 0.05). Binary logistic regression analysis showed the presence of CDHPBR, absence of LM, and poor PC after switching were risk factors for early dose increase (presence of CDHPBR: odds ratios (OR), 3.30, 95% confidence interval (CI), 1.09–9.98; presence of LM: OR, 0.31, 95% CI, 0.10–0.93; good PC: OR, 0.23, 95% CI, 0.07–0.79, respectively). The initial dose increase after switching to FP was earlier in patients with CDHPBR and/or without LM than those without CDHPBR and with LM (p < 0.05, log-rank test). It was suggested that the analgesic effect of FP after switching from OXC is likely to be insufficient in patients treated with CDHPBR and patients without LM.

**Key words** oxycodone tablet; fentanyl patch; opioid switching; risk factor; concomitant drugs with a high protein binding rate; retrospective study

**INTRODUCTION**

Cancers cause serious symptoms with progression in many cases. Since cancer pain develops in about 50% of advanced cancer patients and about 80% of patients in the terminal phase and markedly impairs their QOL, appropriate pain control is very important,1 which requires effective use of strong opioids, therapeutic drugs for cancer pain specified as the 3rd step of the WHO 3-step analgesic ladder.2 At present, strong opioids available in Japan include morphine, oxycodone, fentanyl, methadone, tapentadol, and hydromorphone. Of these, transdermal fentanyl patch is frequently used because it can be used in patients unable to orally ingest, the patch is re-...
drugs (NSAIDs), therapeutic drugs for peripheral neuropathy, cancer chemotherapy, and general drugs with a protein binding rate of 80% or higher and those which induce or inhibit CYP3A4 (Table 1).

(ii) Evaluation of pain control before and after switch

From numerical rating scale, the words of patients, and state of opioid rescue administration, when the patient was not aware of pain or aware of pain but did not require further treatment, pain control was judged as ‘favorable,’ and when the patient was aware of pain and required further treatment, it was judged as ‘poor.’ Pain control after switching was evaluated 2 d after switching and before dose increase. For the laboratory test values, the values measured on the day with the dose described in the package insert was normal, and high dose groups based on the dose described in the package insert. In univariate analysis, the student t-test, Mann–Whitney U-test, Fisher’s exact test, or χ² test was performed using Statcel Ver.2. In multivariate analysis, binary logistic regression analysis was performed using Minitab®16 regarding the early and late increase groups as response variables and factors extracted by univariate analysis as explanatory variables.

To estimate the time (days) to the initial dose increase by the presence or absence of risk factors extracted by multivariate analysis, the Kaplan–Meier curves regarding the initial dose increase earlier than 14 d after switching to fentanyl patch as an event were prepared using EZR®3 and subjected to the log-rank test. The significance level was set at less than 5%.

Ethical Approval This study was approved by the Medical Ethics Committee of Mazda Hospital of Mazda Motor Corporation and Hiroshima Prefectural Hospital.

RESULTS

State of Opioid Administration The subjects were 86 patients and the objective of administration was cancer pain control in all patients. The reason for opioid switching was inability to orally ingest in 38 (44.2%), adverse effects in 23 (26.7%) (nausea: 10, constipation: 7, neuropsychiatric symptoms: 6, others: 2 (including overlapping)), and insufficiency of the effect in 25 (29.1%). The median time (number of days) to the initial dose increase after switching to fentanyl patch was 7.5 d (range: 1–128).

Comparison between the Early and Late Increase Groups The state of pain control by oxycodone tablet before switching to fentanyl patch was favorable in 8 (18.6%) and poor in 35 (81.4%) in the group with early dose increase after switching, and favorable in 23 (53.5%) and poor in 20 (46.5%) in the group with late dose increase after switching, showing a significant difference (p < 0.05, Fisher’s exact test). The state of pain control by fentanyl patch after switching from oxycodone tablet was favorable in 8 (18.6%) and poor in 35 (81.4%) in the group with early dose increase after switching, and favorable in 29 (67.4%) and poor in 14 (32.6%) in the group with late dose increase after switching, showing a significant difference (p < 0.05, Fisher’s exact test).

The median dose of oxycodone tablet before switching to fentanyl patch was 20 mg (range: 10–80) and 20 mg (range: 10–120) in the early and late increase groups, respectively, showing no significant difference (p > 0.05, Mann–Whitney U-test).

The conversion ratio for switching based on comparison with the dose described in the package insert was normal, high, and low dose in 29, 4, and 10 patients, respectively, in the early increase group and 31, 0, and 12, respectively, in the late increase group. No significant difference was noted on comparison of the normal, high, or low dose (p > 0.05, Fisher’s exact test).

Regarding patient background, a significant difference was noted in the presence or absence of liver metastasis between the early and late increase groups (p < 0.05, Fisher’s exact test) (Table 2).

Regarding laboratory test values, no significant difference was noted between the early and late increase groups (p > 0.05, student t-test, Mann–Whitney U-test) (Table 3).

Regarding concomitant drugs, a significant difference was noted in the presence or absence of concomitant drugs with a

Table 1. Major High Protein Binding Rate Drugs, CYP3A4 Inducers and CYP3A4 Inhibitors

| Drug name (Protein binding ratio) | CYP3A4 inducer | CYP3A4 inhibitor |
|----------------------------------|----------------|-----------------|
| Amiodarone (96%)                 | Aprepitant      | Aprepitant      |
| Amitriptyline (94.8 ± 0.8%)      | Asunaprevir     | Atzanavir       |
| Ciclosporin (≥90%)               | Bexotan         | Bromocriptine   |
| Dibutylam (98.1 ± 0.5%)          | Carbamazepine   | Ciclosporin     |
| Diazoxide (90–93%)               | Deferasirox     | Cimetidine      |
| Flurbiprofen (99.9%)             | Dexamethasone   | Clarithromycin  |
| Furosemide (91–99%)              | Efavirenz       | Daranavir       |
| Ibuprofen (99%)                  | Estravine       | Flunonazoloe    |
| Ketoprofen (69.0–84.3%)          | Fosaprepitant   | Fluoxamine      |
| Naproxen (99%)                   | Fosphenytin     | Fosamprenavir   |
| Nifedipine (92–98%)              | Hemin           | Fosaprepitant   |
| Phenytoin (90%)                  | Methadone       | Fosfluonazoloe  |
| Prochlorperazine (≥90%)          | Modafinil       | Indinavir       |
| Propranolol (80.5–95.8%)         | Phenobarbital   | Itraconazole    |
| Quinidine (90%)                  | Phenytoin       | Josamyacin      |
| Tacrolimus (99.0 ± 0.2%)         | Rifabutin       | Quinupristin/Dalfopristin |
| Teicoplanin (90%)                | Rifampicin      | Sineprevir      |
| Tolbutamide (95%)                | Stipiretilon    |                |
| Verapamil (89.6 ± 0.2%)          | Voriconazole    |                |
| (Protein binding ratio was investigated through the interview form.)
Phenytoin (0/1), Prochlorperazine (14/8), Verapamil (1/0). (3 patients with an binding rate drug: Flurbiprofen (2/0), Furosemide (8/6), Naproxen (1/0), Nifedipine pitant (2/1)). CYP3A4 inhibitor: Aprepitant (2/1), Voriconazole (1/0). High protein

ables. The presence of a concomitant drug with a high protein

groups (p < 0.05, Fisher’s exact test) (Table 4). The main concomitant drugs with a high protein binding rate were prochlorperazine maleate tablet and furosemide tablet.

Table 3. Laboratory Values

|                      | Group with an increase in early stage | Group with an increase in late stage | p-Value |
|----------------------|--------------------------------------|--------------------------------------|---------|
| TP (g/dL)            | 6.2 ± 1.0                            | 6.2 ± 0.9                            | 0.98 a) |
| ALT (IU/L)           | 31.8 ± 42.5                          | 34.3 ± 37.3                          | 0.65 b) |
| AST (IU/L)           | 46.7 ± 65.0                          | 49.8 ± 65.8                          | 0.42 b) |
| PLT (x10⁴)           | 135.0 ± 173.1                        | 77.8 ± 117.5                         | 0.073 b) |
| Hb (g/dL)            | 9.9 ± 2.1                            | 10.1 ± 1.8                           | 0.64 a) |
| A/G ratio            | 1.0 ± 0.3                            | 0.98 ± 0.38                          | 0.77 a) |
| Alb (g/dL)           | 2.97 ± 0.65                          | 2.90 ± 0.76                          | 0.66 a) |
| CRE (mg/dL)          | 0.95 ± 0.47                          | 1.18 ± 1.39                          | 0.87 b) |
| T-bil (mg/dL)        | 0.95 ± 1.86                          | 1.06 ± 1.56                          | 0.58 b) |
| CRP (mg/L)           | 7.6 ± 6.1                            | 9.1 ± 8.8                            | 0.73 b) |

Data are presented as the mean ± standard deviation, n, or score. BMI, body mass index; BSA, body surface area. a) Student’s t-test. b) Mann–Whitney’s U-test. c) Chi-square test.

Table 4. Concomitant Drug

|                      | Group with an increase in early stage | Group with an increase in late stage | p-Value |
|----------------------|--------------------------------------|--------------------------------------|---------|
| NSAIDs (+/−)         | 32/11                                | 30/13                                | 0.41 a) |
| Drug of peripheral neuropathy (+/−) | 11/32 | 10/33 | 0.5 a) |
| Chemotherapy (+/−)   | 12/31                                | 16/27                                | 0.25 a) |
| CYP3A4 inducer (+/−) | 2/41                                 | 1/42                                 | 0.5 a)  |
| CYP3A4 inhibitor (+/−) | 3/40 | 1/42 | 0.31 a) |
| High protein binding rate drug (+/−) | 24/19 | 15/28 | 0.041 a) |

a) Fisher’s exact test. Breakdown (early stage/late stage). CYP3A4 inducer: Aprepitant (2/1), CYP3A4 inhibitor: Aprepitant (2/1), Voriconazole (1/0). High protein binding rate drug: Flurbiprofen (2/0), Furosemide (8/6), Naproxen (1/0), Nifedipine (1/0), Phenytoin (1/0), Prochlorperazine (14/8), Verapamil (1/0). (3 patients with an increase in early stage took two of them.)

high protein binding rate between the early and late increase groups (p < 0.05, Fisher’s exact test) (Table 4). The main concomitant drugs with a high protein binding rate were prochlorperazine maleate tablet and furosemide tablet.

Binary logistic regression analysis was performed regarding the early and late increase groups as response variables and factors extracted by univariate analysis as explanatory variables. The presence of a concomitant drug with a high protein binding rate, absence of liver metastasis, and poor pain control after switching were extracted as risk factors for early dose increase (the presence of concomitant drugs: odds ratio, 3.30, 95% confidence interval, 1.09–9.98, p < 0.05; the presence of liver metastasis: odds ratio, 0.31, 95% confidence interval, 0.10–0.93, p < 0.05; favorable control: odds ratio, 0.23, 95% confidence interval, 0.07–0.79, p < 0.05) (Table 5).

Kaplan–Meier curves for the presence or absence of concomitant drugs with a high protein binding rate limiting patients to those with liver metastasis and for the presence or absence of liver metastasis limiting patients to those with concomitant drugs with a high protein binding rate were prepared and subjected to the log-rank test regarding the initial dose increase after switching to fentanyl patch as an event, and a significant difference was noted in both curves (p < 0.05) (Figs. 1, 2).

Furthermore, the test was performed similarly limiting patients to those without liver metastasis and those with concomitant drugs with a high protein binding rate, and a significant difference was noted in both curves (p < 0.05) (Figs. 3, 4).

When patients were limited to those with liver metastasis, the cumulative rate of patients with the initial dose increase of fentanyl patch reached 50% on day 5 after switching in the group with concomitant drugs with a high protein binding rate, whereas it reached 10 day 10 in the group with no concomitant drug with a high protein binding rate. When patients were limited to those with no concomitant drug with a high protein binding rate, the cumulative rate of patients with the initial dose increase of fentanyl patch reached 50% on day 4 in the group without liver metastasis, whereas it reached day 10 in the group with liver metastasis. Furthermore, when

binding rate, absence of liver metastasis, and poor pain control after switching were extracted as risk factors for early dose increase (the presence of concomitant drugs: odds ratio, 3.30, 95% confidence interval, 1.09–9.98, p < 0.05; the presence of liver metastasis: odds ratio, 0.31, 95% confidence interval, 0.10–0.93, p < 0.05; favorable control: odds ratio, 0.23, 95% confidence interval, 0.07–0.79, p < 0.05) (Table 5).

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patients were limited to those without liver metastasis, the cumulative rate of patients with the initial dose increase of fentanyl patch reached 50% on day 3 after switching in the group with concomitant drugs with a high protein binding rate, whereas it was reached on day 4 in the group with no concomitant drug with a high protein binding rate. When patients were limited to those with concomitant drugs with a high protein binding rate, the cumulative rate of patients with the initial dose increase of fentanyl patch reached 50% on day 3 in the group without liver metastasis, whereas it reached day 5 in the group with liver metastasis. Of the 86 patients, 19 only had concomitant drugs with a high protein binding rate (22.1%), 20 had both concomitant drugs with a high protein binding rate and liver metastasis (23.3%), 29 had neither (33.7%), 18 only had liver metastasis (20.9%).

DISCUSSION

For the scale of pain control, focusing on the days to the initial dose increase after switching to fentanyl patch which is thought to be more objective, the patients were divided into 2 groups based on the median time and various items were compared. On binary logistic regression analysis, a causal relationship was noted between early dose increase and poor pain control after switching, which may have validated the study design.

The presence of concomitant drugs with a high protein binding rate was suggested to be a risk factor for poor pain control after opioid switching from oxycodone tablet to fentanyl patch. The number of patients with a concomitant drug with a high protein binding rate was 24 (55.8%) in the early increase group, which was higher than 15 (34.9%) in the late increase group, suggesting that fentanyl was competitively released and elevated the clearance by concomitant drugs with a higher protein binding rate than fentanyl (89.1%). On the other hand, blood level of fentanyl was estimated to be under therapeutic range due to the slow transdermal absorption. General pharmacokinetics of 2 drugs with the following properties competing for the drug binding site of protein have been clarified: orally or intravenously administered drugs with a protein binding rate exceeding 70% and low hepatic extraction ratio, being determined by the intrinsic clearance, and a pro-
tein binding rate exceeding 70% and high hepatic extraction ratio, being determined by blood flow.\(^9\)\(^{10}\) Clearance of fentanyl with a protein binding rate exceeding 70% and high hepatic extraction ratio is determined by blood flow. However, no study on clearance of the drug applied by patch has been reported. It may be necessary to verify the pharmacokinetically presumed findings by measuring the blood level. Prochlorperazine maleate tablet and furosemide tablet were concomitant drugs with a high protein binding rate frequently used for palliative care. The protein binding rate of all the concomitant drugs was higher than fentanyl. Further investigation for other possibilities except for protein binding ratio is necessary.

The absence of liver metastasis was also suggested to be a risk factor. The number of patients without liver metastasis was 30 (69.8%) in the early increase group, which was higher than 18 (41.9%) in the late increase group. It is estimated that patients with liver metastasis maintain a constant hepatic blood flow with increased volume of hepatic artery blood flow and compensatory decreased volume of portal blood flow.\(^9\)\(^{10}\) Although fentanyl is a liver metabolized drug which is dependent on hepatic blood flow, its concentration might be relatively higher because of decreased tissue for drug metabolism in patients with liver metastasis. It may be necessary to verify the pharmacokinetically presumed findings by measuring the blood level.

To estimate the time (days) to the initial dose increase, the conditions before 14 days after switching were analyzed. Firstly, Kaplan–Meier curves for the presence or absence of concomitant drugs with a high protein binding rate limiting patients to those with liver metastasis and for the presence or absence of liver metastasis limiting patients to those with no concomitant drug with a high protein binding rate were prepared regarding the initial dose increase after switching to fentanyl patch as an event and subjected to the log-rank test, and a significant difference was noted in both curves. Then, Kaplan–Meier curves were prepared similarly limiting patients to those without liver metastasis and those with concomitant drugs with a high protein binding rate and subjected to the log-rank test, and a significant difference was noted in both curves. The cumulative rate of patients with the initial dose increase of fentanyl patch reached 50% on day 10 in patients with no risk factor, whereas the rate reached 50% on days 4–5 in patients with one of the risk factors and on day 3 in patients with the 2 risk factors, being earlier, suggesting the necessity of pain control taking dose increase into consideration in the early phase when these risk factors are present, and more careful monitoring is necessary when both risk factors are present.

Poor pain control after switching may be not dose-dependent because there was no significant difference between the early and late increase groups in: 1) the dose of oxycodone tablet before switching and 2) the conversion ratio for switching based on the dose described in the package insert.

Opioid switching was performed due to insufficiency of the effect in 29.1% of the patients, but the state of pain control by oxycodone tablet before switching was not extracted as a risk factor, suggesting that insufficiency of the effect before switching does not influence pain control by fentanyl patch after switching.

No CYP3A4-inducing or -inhibiting influence of concomitant drugs was observed. Only 2 and 1 patients were concomitantly treated with aprepitant capsule and voriconazole tablet, respectively, in the early increase groups, being insufficient to investigate the influence. It was not influenced in a study,\(^{11}\) but further investigation is necessary.

We need to take into account the influence to pain control by primary carcinoma, metastasis, chemotherapy, and chemoradiation. However, those factors may not have affected the results in this study because the median days to the initial dose increase after switching to fentanyl patch was only 7.5 days, and there was no significant difference in carcinoma, bone metastasis, and presence or absence of chemotherapeutic use between the early and late increase groups.

It was suggested that the analgesic effect of fentanyl patch after switching from oxycodone tablet is likely to be insufficient in patients treated with concomitant drugs with a high protein binding rate and patients without liver metastasis, suggesting the necessity of investigation of dose increase from the early phase while paying attention to respiratory depression. Paying attention should be especially necessary for patients with multiple risk factors. We will utilize the list of drugs with a high protein binding rate which showed an influence in actual medical practice in inpatient pharmaceutical service.

**Conflict of Interest** The authors declare no conflict of interest.

**REFERENCES**

1) Sakurai H, Hayashi A. Opioid rotation. Modern Physician, 32, 99–103 (2012).
2) World Health Organization. Cancer Pain Relief, 2nd ed., pp. 15–16 (1996).
3) Hattori S, Sano H, Tanaka K, Yokota M. Opioid rotation: morphine, oxycodone, fentanyl norinsyotekitsukaiwake. Pain Clin., 31, 342–346 (2010).
4) Kodama Y. Touyokeironotekiseikatokanwayakubutsuryohonokouka. Mebio, 30, 67–75 (2013).
5) Kanda Y. Investigation of the freely available easy-to-use software ‘EZR’ for medical statistics. Bone Marrow Transplant., 48, 452–458 (2013).
6) Fentos Tape Japanese package insert.
7) Smith DA, Di L, Kerns EH. The effect of plasma protein binding on in vivo efficacy: misconceptions in drug discovery. Nat. Rev. Drug Discov., 9, 929–939 (2010).
8) Benet LZ, Hoener BA. Changes in plasma protein binding have little clinical relevance. Clin. Pharmacol. Ther., 71, 115–121 (2002).
9) Kunishima S, Taniguchi H, Yamaguchi A, Koh T, Yamagishi H. Changes in hepatic parenchymal blood flow with colorectal metastases: increase in arterial and decrease in portal blood flow. Hepatogastroenterology, 50, 1457–1462 (2003).
10) Leen E, Goldberg JA, Robertson J, Sutherland GR, Hemingway DM, Cooke TG, McArdle CS. Detection of hepatic metastases using duplex/color Doppler sonography. Ann. Surg., 214, 599–604 (1991).
11) Palkama VJ, Neuvonen PJ, Olkkola KT. The CYP 3A4 inhibitor itraconazole has no effect on the pharmacokinetics of i.v. fentanyl. Br. J. Anaesth., 81, 598–600 (1998).