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# 자발적 약물 이상반응 보고 분석을 통한 수술 후 통증 조절에 사용된 Fentanyl의 약물사용적정성

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# Fentanyl PCA Monotherapy and Fentanyl TTS Combination Therapy in Post-Operative Pain Management: Analyses of Spontaneous Adverse Drug Reaction Reports

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## ABSTRACT

**Objective:** There have been many cases of spontaneous adverse drug reactions to fentanyl at a regional pharmacovigilance center in the hospital. To assess the factors causing the adverse drug reactions reported in patients receiving fentanyl patient-controlled analgesia (PCA) monotherapy or in combination with fentanyl transdermal therapeutic system (TTS) for acute post-operative pain management. **Methods:** We conducted a retrospective cohort study with all patients prescribed fentanyl PCA for pain management after orthopedic surgery at a single university hospital from June 2012 to May 2013. We analysed the factors causing adverse drug reactions reported by a spontaneous reporting system in patients receiving fentanyl PCA monotherapy and those receiving fentanyl TTS in combination with fentanyl PCA. **Results:** Based on the spontaneous adverse drug reaction reporting, the risk ratio for the incidence rate of adverse drug reaction in the fentanyl TTS combination therapy group was 3.04 (95 % CI: 2.4–4.00, P 〈 0.0001), which was approximately 3-fold higher than that reported for fentanyl PCA monotherapy. Only 60 % of the adverse drug reactions were reported. **Conclusion:** It is inappropriate to add fentanyl TTS to fentanyl PCA to manage post-operative acute pain. There is a need to improve adverse drug reaction reporting. We expect that regular analysis of adverse drug reactions reported at regional pharmacovigilance centre would aid in appropriate drug utilization by patients.

**KEY WORDS:** Fentanyl PCA, fentanyl TTS, adverse drug reactions, postoperative pain management

About 1,699,265 surgeries were conducted in Korea in 2013, and many patients present with post-operative pain. Approximately 64% of the patients present with severe post-operative pain.[1-2] The common post-operative complication other than pain is post-operative nausea and vomiting (PONV), which has an incidence rate of 32-91%,[3-6] and opioid analgesics used in post-operative pain management can exacerbate PONV.[7] Effective post-operative pain management is an essential component of surgical patient care. Inadequate pain control may result in delayed recovery, decreased pulmonary function, arrhythmia, thromboembolism, myocardial infarction, and chronic pain, which can have an impact on patients' quality of life and increase economic burden and mortality.[8-10] The goal of effective post-operative pain management is to relieve pain, minimize any adverse drug reaction (ADR) related to pain control, and help patients return faster to their everyday life.[10]

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The type of medications for post-operative pain management include opioid analgesics, oral non-narcotic analgesics, patient controlled analgesia (PCA), epidural analgesia, local infiltration analgesia or peripheral nerve block, warm or cold compress, music or relaxation, and other non-pharmacologic methods. Multimodal therapy with different mechanisms or different administration methods is recommended as the best way to manage acute pain after surgery.[11] PCA is one of the most common methods to administer analgesia. The benefit of PCA is that it avoids any unnecessary pain relief below minimum drug concentrations and reduces respiratory depression at peak drug blood level due to frequent administration of opioid analgesics at low doses.[12-13]

Approximately 1,081 spontaneous reports of adverse drug reactions were reported to a regional pharmacovigilance centre (RPVC) at Chung-Ang University Hospital from June 2012 to May 2013, and opioid analgesics ranked as the third most frequently reported drug class (159, 14.7%). Among the reported opioid analgesics, the ADR reporting rates of fentanyl PCA were significantly high with 86 reports (54%); of the 86 reports, combined fentanyl PCA and fentanyl transdermal therapeutic system (fentanyl TTS: Durogesic DTrans®) accounted for 43 (50%) of ADR-reported cases. Fentanyl TTS is used for chronic pain relief when continuous administration of opioid analgesic is needed, and it is not recommended for acute pain relief or post-operative pain relief since it is difficult to control the dose according to the degree of pain. Therefore, we evaluated the combined use of fentanyl PCA and fentanyl TTS after orthopedic surgery. The aim of this study was to assess the ADR rates and spontaneous reporting rates in patients receiving fentanyl PCA alone or combined with fentanyl TTS and to analyse the relative risk (RR) and factors contributing to ADR risk when patients receiving fentanyl PCA were administered fentanyl TTS.

## Method

### Study population

Patients who were prescribed fentanyl PCA after orthopedic surgery from June 2012 to May 2013 at Chung-Ang University Hospital were evaluated. Chung-Ang University Hospital is a tertiary teaching hospital located in Seoul with 900 beds. We included ADRs reported to an RPVC at Chung-Ang University Hospital with a causality assessment scale[14-15] of higher than “possible.” Patients with no electronic medical records were excluded.

### Study design and data source

The study was performed in three steps. First, of the reported ADRs, ADRs related to opioid analgesics were selected and the spontaneously reported ADRs with fentanyl PCA after orthopedic surgery were analysed. The RR and the contributing factors to ADR incidence when fentanyl TTS was added to fentanyl PCA were evaluated from spontaneous ADR reports. Second, a retrospective cohort study was performed by analysing all the cases wherein patients were prescribed fentanyl PCA, which consist of PCA alone or in combination with TTS, and assessing the ADR reporting rates in both groups. Third, in order to assess the actual ADR incidence, which includes those not reported spontaneously, we retrospectively reviewed the medical records of patients administered fentanyl TTS. Two clinical pharmacy specialists independently evaluated the relevant patients’ medical records, and differences in opinions were resolved by an expert ADR consultant.

An ADR is defined as as a noxious response to a drug or combination of drugs, leading to the discontinuation of therapy or a response that gradually subsides upon cessation of therapy. This will confirm the actual ADR incidence rate in patients administered TTS combination therapy and the difference in spontaneous reporting rate. We also evaluated the contributing factor to ADR among patients who reported ADR and those who did not in the TTS combination group. At Chung-Ang University Hospital, fentanyl dose in fentanyl PCA differs according to the type of orthopaedic surgery. To eliminate any discrepancy in analysing this contributing factor, we categorized patients as those with general surgery(the other surgeries) and patients with pelvis, spine, and total knee replacement (TKR) surgery and then performed sub-analysis. We obtained patient’s medication history, age, gender, body mass index (BMI), fentanyl PCA dose, the status of kidney and liver function, fentanyl TTS dose, visual analogue scale (VAS), smoking status, surgical method, duration of surgery, and any ADR reports after PCA administration. This study’s protocol was approved by the Institutional Review Board of Chung-Ang University Hospital.

### Data analysis

Analyses were done with SAS statistical software (version 18.0). General characteristics and medication dose of patients

with spontaneous ADR reports were expressed as a percentage. In order to compare the difference in ADR incidence between the fentanyl PCA group and fentanyl TTS combination group, chi-square tests and Fisher's exact test were used for nominal scale data, Mann-Whitney U test was used for ranking scale data, and Student's *t*-test was used for continuous scale data. Differences were tested using an α level of 0.05.

## Results

The total number of ADRs reported through the pharmacovigilance system in the hospital in the one-year time period was 1,580, and there were 281 ADRs related to narcotics, accounting for 17.8% of those reported. Among them, the number of ADRs reported for fentanyl PCA and TTS combination use after orthopedic surgery was 86 (out of 281) and 51 (out of 281), respectively. Therefore, the total number of spontaneously reported ADRs related to fentanyl PCA was 137 (48.8% of the ADRs related to narcotics in the one-year time period). The 137 ADRs for fentanyl PCA included nausea and vomiting (117, 85.4%), dizziness (13, 9.5%), vertigo (5, 3.6%), chest tightness (1, 0.7%), and sweating (1, 0.7%). General characteristics of ADRs reported by patients are described in Table 1. Their kidney and liver function were within the normal range. The size of the post-orthopedic operative fentanyl PCA prescribed cohort is 1,638. Among these patients, the size of the PCA monotherapy and the TTS combination group was 1,406 (85.8%) and 232 (14.2%), respectively. The ADR incidence rate according to spontaneous ADR reports in the PCA monotherapy group and TTS combination group was 6% and 22%, respectively (Fig. 1). Based on the spontaneous ADR reports, the RR for ADR in the TTS combination group was 3.04 (95% CI: 2.4-4.00, $p<0.0001$), which is 3-fold higher than that reported for the PCA monotherapy group.

In the TTS combination group, additional ADRs were reported in 31(17.1%) patients after reviewing the medical records of 181 patients who had failed to report ADRs spontaneously. The total ADR incidence in the TTS combination group was 82 (35.3%); 51 were from spontaneous reporting and 31 were from medical record reviewing (Fig. 1). Since the ADR incidence rate was 35.3% in the TTS combination group after orthopedic surgery and the spontaneous ADR reporting rate was 22%, the actual ADR incidence and spontaneous ADR reporting rate ratio were approximately 60%.

**Table 1.** General characteristics of patients reporting adverse drug reactions (n = 137)

| Category | | Reported adverse drug reactions, n (%) | | |
|---|---|---|---|---|
| | | PCA[a] | PCA + TTS[b] | Total |
| Sex | Men | 28(62.2) | 17(37.8) | 45(32.8) |
| | Women | 58(63) | 34(37) | 92(67.2) |
| Smoking | Y | 12(57.1) | 9(42.9) | 21(15.3) |
| | N | 74(63.8) | 42(36.2) | 116(84.7) |
| Visual analogue scale | 0 | 11(61.1) | 7(38.9) | 18(13.1) |
| | 1 | 0(0) | 3(100) | 3(2.1) |
| | 2 | 10(47.6) | 11(52.4) | 21(15.3) |
| | 3 | 49(72.1) | 19(27.9) | 68(49.6) |
| | 4 | 2(100) | 0(0) | 2(1.5) |
| | 5 | 4(36.4) | 7(63.6) | 11(8) |
| | 6 | 5(62.5) | 3(37.5) | 8(5.8) |
| | 7 | 3(100) | 0(0) | 3(2.2) |
| | 8 | 1(100) | 0(0) | 1(0.7) |
| | 9 | 0 | 0 | 0 |
| | 10 | 0(0) | 1(100) | 1(0.7) |
| | No data | 1(100) | 0(0) | 1(0.7) |
| Body mass index ($kg/m^2$) | < 20 | 19(70.4) | 8(29.6) | 27(19.7) |
| | 20–25 | 43(62.3) | 26(37.7) | 69(50.4) |
| | 25–30 | 23(62.2) | 14(37.8) | 37(27) |
| | > 30 | 1(25) | 3(75) | 4(2.9) |
| Age (years) Mean ± SD | | 53.03 ± 19.06 | 55.86 ± 19.03 | |
| Fentanyl PCA dose (μg/hour) Mean ± SD | | 1.652 ± 0.29 | 1.586 ± 0.20 | |
| Duration of surgery (minutes) Mean ± SD | | 85.30 ± 51.60 | 91.00 ± 49.38 | |
| ADR onset after PCA (hours) Mean ± SD | | 12.16 ± 16.06 | 17.98 ± 15.48 | |

[a]Patients prescribed fentanyl PCA only
[b]Patients prescribed both fentanyl PCA and fentanyl TTS

To investigate the contributing factors to ADR in the TTS combination group, we compared gender, smoking status, visual analogue scale (VAS) score, body mass index (BMI), age, fentanyl PCA dose, fentanyl TTS dose, duration of surgery in patients with ADR reported (82, 35.3%), and number of patients with no ADR reported (Table 2). No other contributing factors other than VAS (p=0.040) and duration of surgery (p=0.03) showed significant differences. The ADR incidence rate according to fentanyl TTS dose was investigated. The ADR incidence rate in patients receiving 12 and 25 mcg/h fentanyl TTS was 4 (18.1%) and 78 (37.1%), respectively. The

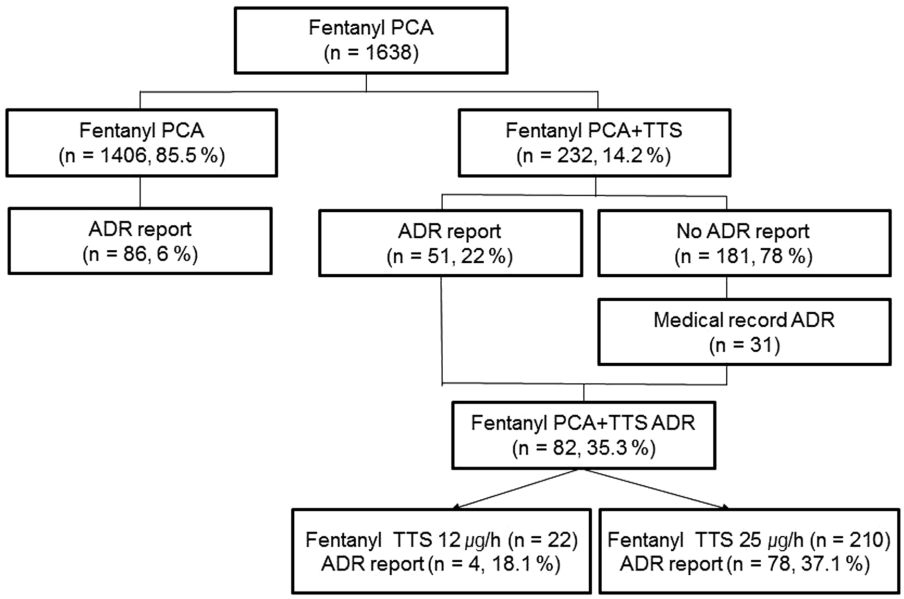


**Fig. 1.** ADR reports with fentanyl PCA monotherapy and fentanyl PCA and TTS combination therapy *PCA* Patient controlled analgesia, *TTS* Transdermal therapeutic system, *ADR* adverse drug reactions

prescription rate of high-dose fentanyl TTS among ADR reporting patients was high, but it was not significantly different (p=0.101).

The degree of pain differs according to the type of surgery, and it could affect the dose of the analgesic. Thus, we investigated the contributing factors through adjusted analysis. Surgeries were categorized into pelvis; spine; total knee replacement (TKR) surgery; and general surgery, and analyses according to different surgeries were conducted. The correlation between adverse effect and spine, pelvis, and TKR surgery is described in Table 3. The correlation for VAS was significantly different between the ADR reported group and non-ADR reported group p=0.001). ADR was reported to differ with age. No correlation was observed between fentanyl PCA dose and ADR (p=0.076); however, the ADR incidence showed a significant difference with duration of surgery (p =0.003). A total of 87 patients underwent general surgery, and only fentanyl PCA dose and ADR incidence showed a significant correlation in this group, as described in Table 3 (p =0.017).

## Discussion

We assessed the inappropriate use of fentanyl TTS in combination with fentanyl PCA, which is used to manage acute post-operative pain, by reviewing spontaneous ADRs reported to an RPVC in patients receiving fentanyl PCA monotherapy and those receiving fentanyl TTS in combination. The ADR reporting rate in regards to fentanyl PCA was 2-fold higher in women than in men and was also higher in the smoking group, which is in line with the results of other studies.[16-18] Among the ADRs in fentanyl PCA patients, nausea and vomiting accounted for approximately 87.4%, which is higher than that reported by another study (52–62%).[11] We assume that this is attributable to combination use with fentanyl TTS in this study[10]. Assessment of the ADR risk ratio based on the actual spontaneous ADR reports showed that the ADR risk ratio was 3.04 (95% CI: 2.4–4.00, p<0.0001) and that it is 3-fold higher in the TTS combination group than in fentanyl PCA monotherapy group.

At Chung-Ang University Hospital, where this study was conducted, fentanyl PCA and fentanyl TTS were used in combination for post-operative pain management; however, there is little evidence for use of fentanyl TTS for post-operative pain management.[19] The European Association of Urology guideline suggests the use of fentanyl ITS (fentanyl HCL iontophoretic transdermal system); however, fentanyl ITS only allows drug delivery at a pre-determined dose, which is different from fentanyl TTS (Durogesic DTrans®), which allows continuous drug delivery to maintain a certain blood level.[20] In addition, it is difficult to rationalize the use of

**Table 2.** Correlation between adverse drug reactions and several surgery factors in the combination therapy of fentanyl PCA and TTS (n = 232)

| Category | | Adverse drug reactions, n (%) | | p value |
|---|---|---|---|---|
| | | Yes (n = 82) | No (n = 150) | |
| Sex | Men | 30(30.6) | 68(69.4) | 0.197 |
| | Women | 52(38.8) | 82(61.2) | |
| Smoking | Yes | 18(35.3) | 33(64.7) | 0.993 |
| | No | 64(35.4) | 117(64.6) | |
| Visual analogue scale | 0 | 8(44.4) | 10(55.6) | 0.040 |
| | 1 | 6(66.7) | 3(33.3) | |
| | 2 | 16(43.2) | 21(56.8) | |
| | 3 | 34(31.2) | 75(68.8) | |
| | 4 | 1(16.7) | 5(83.3) | |
| | 5 | 9(42.9) | 12(57.1) | |
| | 6 | 5(33.3) | 10(66.7) | |
| | 7 | 1(14.3) | 6(85.7) | |
| | 8 | 0(0) | 7(100) | |
| | 9 | 0(0) | 0(0) | |
| | 10 | 2(66.7) | 1(33.3) | |
| Body mass index ($kg/m^2$) | < 20 | 8(32) | 17(68) | 0.589 |
| | 20-25 | 46(38.3) | 74(61.7) | |
| | 25-30 | 23(34.3) | 44(65.7) | |
| | > 30 | 4(22.2) | 14(77.8) | |
| Age (years) Mean ± SD | | 57.50 ± 17.91 | 56.97 ± 16.47 | 0.822 |
| Fentanyl TTS dose | 12 mcg/h | 4(18.2) | 18(81.8) | 0.101 |
| | 25 mcg/h | 78(37.1) | 132(62.9) | |
| Fentanyl PCA dose (μg/hour) Mean ± SD | | 1.59 ± 0.224 | 1.60 ± 0.201 | 0.659 |
| Duration of surgery (minutes) Mean ± SD | | 99.28 ± 50.46 | 126.37 ± 73.62 | 0.003 |

fentanyl TTS in combination with fentanyl PCA, since they both contain the same ingredient.

When the contributing factors for ADRs were assessed, VAS score and duration of surgery showed significant differences. The VAS score especially was significantly low in patients with ADRs, suggesting that a higher dose of fentanyl had been prescribed for higher degrees of pain. The duration of surgery showed a significant difference as well; however, this needs careful interpretation since there was no differentiation with regard to type of surgery. The ADR incidence rate in patients with pelvis, spine, and TKR surgeries differed according to the VAS score, age, and duration of surgery. ADR reporting was higher for patients with lower VAS score, indicating that the fentanyl dose administered was higher than required. For the duration of surgery, we cannot exclude the impact of additional confounding factors since it was assessed without distinguishing the type of surgery (e.g., pelvis, spine, TKR).

We found additional ADRs in 31 patients after reviewing the medical records of patients prescribed TTS in combination with PCA, which shows that only 60% of actual ADRs are being reported to RPVC. Assessment of ADRs that are not recorded in medical records showed that the number of missing ADRs being reported would be higher. Therefore, more effort should be exercised for active reporting of ADRs.

Our study had some limitations. We assessed the degree of post-orthopedic operative pain management by fentanyl PCA only and in combination with fentanyl TTS and the ADR incidence rate by retrospectively reviewing the spontaneous ADR reports and patients' medical records. We did not assess the use of other analgesics, such as NSAIDs, and only focused on fentanyl PCA and fentanyl TTS; therefore, a further study that includes the assessment of non-narcotic analgesics needs to be conducted. However, we confirmed that use of fentanyl TTS is a contributing factor to ADR incidence risk after assessing the appropriateness of fentanyl TTS use in combination with fentanyl PCA for post-operative pain management.

**Table 3.** Correlation between adverse drug reactions and surgery types in the combination therapy of fentanyl PCA and TTS

| Orthopedic surgery type | | Spine, Pelvis, TKR surgery (n = 145) | | | General surgery (n=87) | | |
|---|---|---|---|---|---|---|---|
| Category | | Adverse drug reactions (n, %) | | p value | Adverse drug reactions (n, %) | | p value |
| | | Yes (n = 48) | No (n = 97) | | Yes (n = 34) | No (n = 53) | |
| Sex | Men | 13(25) | 39(75) | 0.121 | 17(37) | 29(63) | 0.667 |
| | Women | 35(37.6) | 58(62.4) | | 17(41.5) | 24(58.5) | |
| Smoking | Yes | 8(32) | 17(68) | 0.897 | 10(38.5) | 16(61.5) | 0.938 |
| | No | 40(33.3) | 80(66.7) | | 24(39.3) | 37(60.7) | |

**Table 3.** Correlation between adverse drug reactions and surgery types in the combination therapy of fentanyl PCA and TTS (continued)

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Visual analogue scale | 0 | 5(38.5) | 8(61.5) | 0.001 | 3(60) | 2(40) | 0.554 |
| | 1 | 5(71.4) | 2(28.6) | | 1(50) | 1(50) | |
| | 2 | 11(52.4) | 10(47.6) | | 5(31.3) | 11(68.8) | |
| | 3 | 22(30.6) | 50(69.4) | | 12(32.4) | 25(67.6) | |
| | 4 | 0(0) | 3(100) | | 1(33.3) | 2(66,7) | |
| | 5 | 4(36.4) | 7(63.6) | | 5(50) | 5(50) | |
| | 6 | 1(11.1) | 8(88.9) | | 4(66.7) | 2(33.3) | |
| | 7 | 0(0) | 5(100) | | 1(50) | 1(50) | |
| | 8 | 0(0) | 3(100) | | - | 4(100) | |
| | 9 | 0(0) | 0(0) | | - | - | |
| | 10 | 0(0) | 1(100) | | 2(100) | - | |
| Body mass index ($kg/m^2$) | <20 | 3(25) | 9(75) | 0.687 | 5(38.5) | 8(61.5) | 0.720 |
| | 20-25 | 28(37.8) | 46(62.2) | | 18(39.1) | 28(60.9) | |
| | 25-30 | 13(28.9) | 32(71.1) | | 10(45.5()) | 12(54.5) | |
| | >30 | 3(25) | 9(75) | | 1(16.7) | 5(83.3) | |
| Age (yearts) Mean±SD | | 65.33±14.26 | 59.61±16.95 | 0.046 | 46.44±16.80 | 52.13±14.48 | 0.096 |
| Fentanyl TTS dose No. (%) | 12 mcg/h | 3(18.8) | 13(81.3) | 0.265 | 1(16.7) | 5(83.3) | 0.265 |
| | 25 mcg/h | 45(33.3) | 84(65.1) | | 33(40.7) | 48(59.3) | |
| Fentanyl PCA dose (μg/hour) Mean±SD | | 16.27±2.42 | 17.06±2.58 | 0.076 | 15.29±1.83 | 14.15±2.54 | 0.017 |
| Duration of surgery (minutes) Mean±SD | | 102.88±54.19 | 140.93±79.52 | 0.003 | 94.21±44.97 | 99.72±52.33 | 0.614 |

PCA:patient-controlled analgesia, TTS: transdermal therapeutic system, TKR: total knee replacement

## Conclusion

Effective post-operative pain management is an essential component to improve patients' quality of life. It is inappropriate to add fentanyl TTS, which is prescribed to manage chronic pain, to fentanyl PCA to manage post-operative acute pain. Adding fentanyl TTS to fentanyl PCA increased the ADR incidence risk by 3-fold. Regular analysis of spontaneous ADRs, as shown in this study, would help in the surveillance of safe use of medications and help raise awareness to increase spontaneous ADR reporting.

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