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# Population pharmacokinetics and analgesic potency of fentanyl in surgical patients

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# Population pharmacokinetics and analgesic potency of fentanyl in surgical patients

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## ABSTRACT

**Background:** We aimed to characterize the population pharmacokinetics of fentanyl in surgical patients and to determine the minimum effective concentration (MEC) and minimum effective analgesic concentration (MEAC) of intravenous fentanyl in patients after major abdominal open surgery. We also calculated the equianalgesic concentration ratio of oxycodone to fentanyl by using the median MEAC value of oxycodone observed in our previous study.

**Methods:** In the pharmacokinetic study, patients received an intravenous bolus of 100 μg fentanyl during operation, and arterial blood was sampled at pre-set intervals. In the analgesic-potency study, patients were asked to rate their pain every 10 min using a visual analogue scale (0 = no pain, 10 = most severe pain) in the postanesthesia care unit. The first blood sample was obtained when wound pain was rated as ≥ 3 at rest and ≥ 5 during compression. Then, 50 μg fentanyl was administered every 10 min until the pain intensity had decreased to < 3 at rest and < 5 during compression, at which point the second blood was sampled and the 1st MEAC of fentanyl was measured. The same procedure was repeated to obtain a third sample (MEC) and fourth sample (2nd MEAC).

**Results:** In the population pharmacokinetic study (n = 30), the plasma concentration of fentanyl over time was well-described by the three-compartment mammillary model using an allometric expression. In the analgesic-potency study (n = 30), the median MEC was 0.72 ng/ml, and the MEACs were 0.97 ng/ml and 1.04 ng/ml at 1st and 2nd measurement, respectively.

**Conclusion:** These results provide a scientific basis for the use of fentanyl for acute postoperative pain management in surgical patients. The equianalgesic concentration ratio and equipotent ratio of oxycodone to fentanyl were 75:1 and 100:1, respectively.



**Keywords**: Analgesia, Model, Fentanyl, Pharmacokinetic, Potency

Contents

Lists of Tables and Figures

## INTRODUCTION

Fentanyl is a class of opioid commonly used for postoperative pain control and as an adjunct to general anesthesia. The pharmacokinetics of fentanyl has a wide interindividual variability,[1,2] which can be quantified by population analysis using the nonlinear mixed effects model (NONMEM).[3] However, the pharmacokinetic parameters of intravenous fentanyl have been mainly determined by noncompartmental analysis in healthy volunteers.[4-6] Quantitative characterization of fentanyl pharmacokinetics using population analysis in surgical patients may be needed to properly administer intravenous fentanyl in such patients by taking into account the considerable interindividual variability of the opioid.

The analgesic effect of fentanyl is closely related to its plasma concentrations.[7] Therefore, maintaining fentanyl plasma concentrations between the minimum effective concentration (MEC, indicated by the need for administering intravenous fentanyl due to pain) and the minimum effective analgesic concentration (MEAC, indicated by relief of pain by administering fentanyl) can be effective for adequate treatment of postoperative pain. The MEC and MEAC values of opioids may vary depending on the type of surgery, method of evaluation, and intensity of pain at the time of assessment.[8-10] The MEAC of fentanyl was reported as 0.6–1 ng/ml,[7] but the evidence for this result was somewhat vague. The MEC and MEAC of fentanyl need to be identified in patients who have undergone major abdominal open surgery,

which induces severe postoperative pain.

The aims of this study were to characterize the population pharmacokinetics of fentanyl following a single intravenous bolus of 100 μg in surgical patients and to determine the MEC and MEAC of intravenous fentanyl for major abdominal open surgeries (e.g., gastric, colorectal, and hepatobiliary surgeries). In addition, we calculated the equianalgesic concentration ratio of oxycodone to fentanyl by comparing the median MEAC value of oxycodone, which was described in our previous similarly-designed study on oxycodone.

## MATERIALS & METHODS

### Patient population

This study was approved by the Institutional Review Board (Asan Medical Center, Seoul, Korea, approval number: 2018-1103, approval date: September 22, 2018) and registered on an international clinical trials registry platform (http://cris.nih.go.kr, KCT0003273, principal investigator: Byung-Moon Choi, date of registration: October 18, 2018) prior to enrollment of the first subject. The study consisted of two clinical trials—a population pharmacokinetic study (n=30) and an analgesic potency study (n=30). Written informed consent was obtained from all participating patients. The patients were enrolled in the pharmacokinetic and analgesic-potency studies during November 2018–February 2019 and November 2018–December 2018, respectively. Inclusion criteria were age between 20 and 80 years and American Society of Anesthesiologists physical status classification I and II. Exclusion criteria were as follows: history of allergic response to fentanyl, long-term use of opioid medications, hemoglobin level less than 9 g/dl, pregnancy, history of hepatic, cardiopulmonary or renal disease, or history of chronic pain. Also, patients undergoing laparoscopic surgery were excluded from the analgesic potency study.

### Study procedures

All patients fasted for 6–8 h prior to surgery without premedication. In the operating

room, all patients were monitored with electrocardiogram, pulse oximetry, non-invasive blood pressure, train-of-four (TOF), end-tidal carbon dioxide partial pressure (Carescape B850; GE Healthcare, Milwaukee, Wisconsin, USA), and the bispectral index (BIS monitor; Covidien, Boulder, Colorado, USA). Anesthesia was induced and maintained with target effect-site concentration-controlled infusion of propofol and remifentanil (Perfusor® Space; B. Braun Melsungen AG, Melsungen, Germany).[11,12] Tracheal intubation was performed after administration of 0.6 mg/kg rocuronium. A 20-gauge catheter was inserted into a radial artery for frequent blood sampling. The target concentrations of propofol and remifentanil were adjusted to maintain BIS values at less than 60 and stable hemodynamics (systolic blood pressure > 80 mm Hg; heart rate > 45 beats/min), respectively. Intravenous patient-controlled analgesia (IV PCA) with oxycodone was used for postoperative pain control. Semi-electronic pump (AutoMed 3200; Ace Medical, Seoul, Korea) was used for PCA with a demand bolus of 1 ml, background infusion of 1 ml/h and lock-out time of 15 min. The concentration of oxycodone in IV PCA bag was 1 mg/ml, and 200 ml of oxycodone-normal saline mixture was delivered to patients over 3–4 days.

**Intervention for the pharmacokinetic study**

Patients received a single intravenous bolus of 100 μg fentanyl citrate (Hana

Pharmaceutical, Co., Ltd., Seoul, Korea.) before skin incision. A total of 14 arterial blood samples (5 ml each) were obtained at pre-set intervals thereafter (0, 1, 2, 4, 6, 10, 30, 60, and 90 min, and 2.5, 5.5, 7, 9, and 12 h) to measure the fentanyl concentration in the plasma.

**Intervention for the analgesic potency study**

Patients received fentanyl (1 μg/kg) 30 min before the end of surgery. After the end of surgery, tracheal extubation was performed when the TOF ratio was greater than 0.9 and the BIS value was greater than 80. Patients were transported to the post-anesthesia care unit (PACU), where their state of consciousness was assessed with a modified Aldrete score.[13] Electrocardiogram, pulse oximetry, and non-invasive blood pressure were also monitored. Thereafter, the patients were assessed for pain every 10 min using a visual analogue scale (VAS) (0 = no pain; 10 = the most severe pain). Pain was measured at rest and when the wound areas were compressed with a force of 20 N (i.e., 2 kg of pressure imposed by three fingers on a 10 $cm^2$ area);[14] the wound compression was performed by a researcher who was trained with an algometer (Commander Algometer, J Tech Medical Industries, Midvale, UT, USA) for consistent application of force. When wound pain was rated as ≥ 3 at rest or ≥ 5 during compression, the first venous blood sample was obtained. The patients were then administered with 50 μg intravenous fentanyl every 10 min until the VAS

assessments showed that the pain intensity had decreased to < 3 at rest and < 5 during compression. At this point, the second blood sample was obtained, and the first MEAC of fentanyl was measured.[8] Thereafter, pain was evaluated every 10 min. When wound pain was rated as ≥ 3 at rest or ≥ 5 during compression, the third venous blood sample was obtained, and the MEC of fentanyl was measured.[8] The patients were then administered with 50 μg intravenous fentanyl every 10 min until the pain intensity had decreased to < 3 at rest and < 5 during compression. At this point, the fourth blood sample was obtained, and the second MEAC of fentanyl was measured.

**Blood sample acquisition and assay**

Blood samples were collected in ethylene-diamine-tetraacetic acid (EDTA)-containing tubes and centrifuged for 10 min at 1500 × g. The plasma was stored at −70℃ until used for assay. Plasma concentrations of fentanyl were analyzed using an ultrafast liquid chromatography (UFLC) system (Shimadzu, Kyoto, Japan) coupled with tandem mass spectrometry (API5500, SCIEX, Framingham, MA, USA). A Luna Phenyl-hexyl column (Phenomenex, Torrance, CA, USA) was used for chromatographic separation. The mobile phase consisted of a mixture of 10 mM ammonium formate (with 0.1% formic acid) in water and acetonitrile (50:50, v/v), and a flow rate of 0.3 mL/min was used. The column oven temperature was

maintained at 40℃, and the injection volume was 2 μL. Ion pairs of m/z 337.244 → 188.000 for fentanyl and m/z 380.300 → 91.100 for the internal standard were selected for quantitation. The validated quantification range was 0.01–20 ng/ml. The lower limit of quantification (LLoQ) was 0.01 ng/ml. The within-run accuracy ranged from 90.0% to 110.0%, and the between-run accuracy ranged from 96.7% to 103.3%. The within-run and between-run precision levels, expressed as % coefficient of variation (CV), were < 11.1% and < 10.0%, respectively.

**Non-compartmental analysis of fentanyl**

Fentanyl concentration-time data were fit by noncompartmental methods to determine the $AUCl_{ast}$ (area under the curve from administration to the last measured concentration), $AUC_{inf}$ (area under the curve from administration to infinity), and $\lambda z$ (apparent terminal rate constant) using the Phoenix 64/WinNonLin software (Certara USA, Inc., Princeton, NJ, USA)

**Population pharmacokinetic analysis**

The population pharmacokinetic analysis was performed with NONMEM VII level 4 (ICON Development Solutions, Ellicott City, MD, USA). Fentanyl concentrations were fitted to one-, two-, and three-compartment mammillary models using the ADVAN13 subroutines and first-order conditional estimation with interaction. A log-

normal model was used to estimate the inter-individual random variabilities (IIVs) of pharmacokinetic parameters, and diagonal matrices were applied to estimate the various distributions of η, where η represented the IIV. Constant CV residual error model was applied to the model building. NONMEM computed the minimum objective function value (OFV), a statistical equivalent to the −2 log-likelihood of the model. An α level of 0.05, which corresponded to a reduction in the OFV of 3.84 (Chi-square distribution, degrees of freedom = 1, $P < 0.05$), was used to distinguish between hierarchical models.[15] The fit of the data was also tested by allometric expression.[16] The analyzed covariates were weight, height, age, sex, body surface area,[17] body mass index, ideal body weight,[18] free fat mass,[19] and albumin. Non-parametric bootstrap analysis served to internally validate the models (fit4NM 3.3.3, Eun-Kyung Lee and Gyu-Jeong Noh; http://cran.r-project.org/web /packages/fit4NM/index.html; last accessed: March 16, 2011).[20] Predictive checks were also performed using the fit4NM 3.3.3.[20]

**Determination of analgesic potency using logistic regression**

To determine analgesic potency, pain was defined as the need for additional fentanyl administration. No pain was defined as situations in which administration of rescue fentanyl was not required. Every measured plasma fentanyl concentration was joined to 0 (Pain, 1$^{st}$ and 3$^{rd}$ samples) or 1 (No pain, 2$^{nd}$ and 4$^{th}$ samples). The relationship

between the probability of analgesia and the measured plasma fentanyl concentration was analyzed using a sigmoid $E_{max}$ model:

$$\text{Probability of analgesia} = \frac{C_p^{\gamma}}{C_{p50}^{\gamma} + C_p^{\gamma}}$$

, where $Cp$ is the measured plasma fentanyl concentration, $Cp_{50}$ is the plasma concentration associated with a 50% probability of analgesia, and $\gamma$ is the steepness of the concentration vs. response relation. The likelihood (L) of the observed response (R) was described by the following equation:

$$\text{Likelihood} = R \times \text{Prob} + (1 - R) \times (1 - \text{Prob})$$

, where Prob is the probability of analgesia. Model parameters were estimated using the option "LIKELIHOOD LAPLACE METHOD = conditional" in NONMEM. The IIVs of $C_{p50}$ and $\gamma$ were modeled using a log-normal model.

**Simulation**

Based on the MEC and MEAC measured from the analgesic potency study and pharmacokinetic parameters estimated from the population pharmacokinetic study, fentanyl dosing regimens for postoperative pain management in the PACU were simulated in hypothetical patients with varying weights. Deterministic simulations that considered neither the interindividual nor the intra-individual random variability were performed using simulation program (Asan Pump, version 2.1.3, Bionet Co.,

Ltd., Seoul, Korea).

**Equianalgesic concentration ratio and equipotent ratio of oxycodone to fentanyl**

In the same design as the fentanyl study, the study on population pharmacokinetics and analgesics potency of oxycodone was conducted in a similar manner with a previous study.[14] The study design of analgesic potency was identical except that the doses of oxycodone administered as rescue analgesics in the PACU were different. Patients received 2 mg intravenous oxycodone (body weight < 80 kg) or 3 mg (> 80 kg) every 10 min until the pain intensity had decreased to < 3 at rest and < 5 during wound compression according to the VAS assessments.[14] The same investigator evaluated wound compression pain in both studies. The equianalgesic concentration ratio was calculated by comparing the median MEACs of fentanyl and oxycodone in each study. The equipotent ratio of fentanyl to oxycodone was also calculated by comparing the $Cp_{50}$ obtained from pharmacodynamic analysis using logistic regression.

**Statistical Analysis**

Statistical analysis was conducted using the SigmaStat software version 3.5 for Windows (Systat Software, Inc., Chicago, IL, USA). The four concentrations (1$^{st}$ sample, 2$^{nd}$ sample [1$^{st}$ MEAC], 3$^{rd}$ sample [MEC], 4$^{th}$ sample [2$^{nd}$ MEAC]) obtained

in the analgesic potency study were compared using the Friedman repeated measures analysis of variance (ANOVA) on rank followed by a post-hoc Tukey test. The data are expressed as means (SDs) for normally distributed continuous variables, medians (25–75%) for non-normally distributed continuous variables, and counts and percentages for categorical variables. *P* values < 0.05 were considered statistically significant.

## RESULTS

### Patient population

A total of 32 patients were initially enrolled in the pharmacokinetic study, and two patients were dropped out due to withdrawal of consent prior to fentanyl administration (n = 1) and cancellation of elective surgery (n = 1). A total of 31 patients were initially enrolled in the analgesic potency study, and one patient dropped out due to withdrawal of consent. Hence, 60 patients were included in this study as a whole (pharmacokinetic study: n = 30; analgesic potency study: n = 30). Characteristics of the patient populations are shown in table 1.

### Non-compartmental analysis

In total, 420 blood samples were obtained from 30 patients. Three of these samples were excluded from the analysis due to overly high fentanyl concentration (514.1 ng/ml) at 10 min after a single intravenous bolus of 100 μg fentanyl in one patient (ID25) and low fentanyl concentration below the LLoQ in two patients (ID6 and ID29). Hence, 417 plasma concentration measurements were used to characterize the pharmacokinetics of fentanyl. Plasma concentrations of fentanyl over time are shown in figure 1A. In two patients (ID15 and ID21), fentanyl was inadvertently administered in the PACU for pain control and an elevation of concentration was observed around 420 min. In all other patients, exponential decreases in fentanyl

concentration over time were observed. The mean (SD) $AUC_{last}$ and $AUC_{inf}$ were 124.9 (28.4) min·ng/ml and 142.3 (35.1) min·ng/ml, respectively. The mean (SD) λz was 0.17 (0.07) 1/h. Except in three patients, at least 80% of the total area under the curve was covered by the measured concentrations (11.7% of $AUC_{\%Extra}$, percentage of the extrapolated area under the curve to the total area under the curve).

**Population pharmacokinetics of fentanyl**

The three-compartment model best described the pharmacokinetics of fentanyl in surgical patients. The parameter estimates of the competing base and covariate pharmacokinetic models of fentanyl are described in table 2. The model that applied the allometric expression was selected as the final model. Table 3 shows the population pharmacokinetic parameter estimates and the results of nonparametric bootstrap replicates of the final pharmacokinetic model of fentanyl. The bootstrap replicates and the final model parameter estimates had similar median values. Goodness-of-fit plots of the final pharmacokinetic model of fentanyl are presented in figure 1B–D. Overall, no significant bias was observed. Predictive checks of the final pharmacokinetic model are presented in figure 2. In total, 10.9% of the data were distributed outside of the 90% prediction intervals of the predictive check, indicating that the final model was adequate for describing the time-courses of fentanyl plasma concentrations.

**MEC, MEAC, and analgesic potency of fentanyl**

Total doses of 250 (100–350) μg and 50 (50–100) μg of fentanyl were required to achieve the first and second MEAC, respectively. A total of 120 plasma concentration measurements from 30 patients were used to determine the MEC and MEAC and to perform the logistic regression analysis. When patients arrived at the PACU and complained of pain, their median (25–75%) plasma concentration of fentanyl at the first blood sample was 0.15 (0.13–0.17) ng/ml. The median plasma concentration of fentanyl at the second blood sample (MEC) was 0.72 (0.58–1.05) ng/ml. At the first and second pain relief ($1^{st}$ MEAC and $2^{nd}$ MEAC), the median plasma concentrations of fentanyl were 0.97 (0.70–1.20) ng/ml and 1.04 (0.81–1.34) ng/ml, respectively (fig. 3A). The relationship between the probability of analgesia and the measured plasma fentanyl concentration is shown in figure 4A. The estimates of $Cp_{50}$ (SE) and γ (SE) were 0.63 (0.05) ng/ml and 2.24 (0.24), respectively. The η estimates for both parameters were too small ($Cp_{50}$: 9.75E−15, γ: 4.33E−15) to fix the η to zero.

**Simulation**

The fentanyl dosing regimens for managing postoperative pain in the PACU were described for hypothetical patients with varying weights (fig. 5). Fentanyl 50 μg was

administered 30 min before transfer to the PACU, and the demand bolus of intravenous patient-controlled analgesia (PCA) was assumed to be 15 μg. It was also assumed that the patient stayed in the PACU for approximately one hour. For patients weighing less than 50 kg, one dose of 50 μg fentanyl was administered as a rescue analgesic in the PACU, and the demand bolus was given once before the patient went to the general ward. For patients weighing more than 50 kg and less than 80 kg, two doses of 50 μg fentanyl were required in the PACU. For patients weighing more than 80 kg, three doses of 50 μg fentanyl were administered to maintain the plasma concentrations of fentanyl at above the MEC.

**Equianalgesic concentration ratio and equipotent ratio of oxycodone to fentanyl**

The first and second median (25−75%) MEACs of oxycodone were 74.1 (62.3–90.0) ng/ml and 76.1 (70.9–91.4) ng/ml, respectively (fig. 3B).[14] The equianalgesic concentration ratio of oxycodone to fentanyl was 75:1, and the estimates of $Cp_{50}$ (SE) of oxycodone was 59.9 (2.4) ng/ml (fig. 4B).[14] The equipotent ratio of oxycodone to fentanyl was approximately 100:1.

## DISCUSSION

Changes in plasma concentrations of fentanyl over time after a single bolus of fentanyl were well-explained by a three-compartment mammillary model using an allometric expression. In patients who had major abdominal open surgeries, the median MEC and MEAC of fentanyl in the PACU were 0.7 and 1.0 ng/ml, respectively. The equianalgesic concentration ratio and equipotent ratio of oxycodone to fentanyl were 75:1 and 100:1, respectively.

The interindividual variability of pharmacokinetic parameters is commonly described by body size including weight.[11,21] Allometry, which explains the relationship of body size to shape, could help develop a model that well-predicts remifentanil concentration for a wide range of age and weight of patients.[16] Traditionally, the allometric exponents of volumes and clearances had been fixed at 1 and 0.75;[16] however, estimating these allometric exponents sometimes even further reduced the objective function value.[22] In our study, the model for estimating allometric exponents also reduced the objective function value more than did the model fixed at the traditional value. Unfortunately, previous studies that explored the pharmacokinetics of intravenous fentanyl using nonlinear regression analysis did not include covariates in the pharmacokinetic parameters.[1,23] Considering the weight-based administration of fentanyl in clinical settings, it may be reasonable to include body weight as a covariate of pharmacokinetic parameters of fentanyl. One report

showed that the metabolic clearance of fentanyl was lower in older people [(*Cl*: 991 ± 111 ml/min for adults (n=5), 275 ± 57 ml/min for elderly (n=4)],[24] but other studies have not reported such age-related differences in metabolic clearance.[25,26] Likewise, in our study, age was not a significant covariate in metabolic clearance.

In the analgesic potency study, the fentanyl plasma concentration of the 3rd blood sample (MEC) was about six times higher than that of the 1st blood sample. This indicates that the loading dose of fentanyl administered during surgery was not enough, and that the plasma concentration of fentanyl was low at the time of transfer to the PACU. For this reason, patients complained of pain that required rescue analgesics after arrival at the PACU. Previous studies have incorrectly defined the 1st and 3rd blood sample concentrations in the PACU as the 1st and 2nd MECs:[8,14] the 1st blood sample concentration is not the 1st MEC, but actually any concentration below the MEC, and the 3rd blood sample is the actual 1st MEC. Therefore, we corrected the figure from a previous oxycodone study and presented it in figure 3B. Considering that the two measured MEAC values were similar, the MEAC could be regarded as reliable. The MEAC value of fentanyl determined in our study fall within the range of MEAC (0.6–1.0 ng/ml) reported in a previous study.[7] In that previous study,[7] the type of surgery, evaluation method, and timing of evaluation used to determine MEAC were not clear.

No studies have explicitly examined the MEAC of fentanyl after laparoscopic

surgery. However, as we observed that the MEAC of fentanyl in the PACU was 1 ng/ml in patients who underwent major abdominal open surgery, it may be assumed that the MEAC of fentanyl after laparoscopic surgery would be lower than 1 ng/ml. In addition, as postoperative pain decreases over time, the MEAC of fentanyl measured in the general ward at 1–2 days after surgery may be lower. As such, the MEAC value of fentanyl determined in this study may be the upper reference value for postoperative pain control in surgical patients.

Opioid rotation, defined as switching from one opioid to another or changing the administration route of an opioid, has become an effective method for optimizing pain management in postsurgical patients and cancer patients.[27] To perform opioid rotation in clinical situations, it is necessary to calculate an approximate analgesic dose because the analgesic potency of opioids varies greatly.[28] Relative potency, defined as the ratio of opioid doses necessary to obtain roughly equivalent effects, has been determined through clinical trials that compared among different opioids.[28] The most reliable method for determining the relative potency is evaluating pain after an intravenous bolus of an opioid.[27] Relative analgesic potency can be converted into equianalgesic doses by applying the dose ratio to a standard opioid;[28] this calculation is based on the assumption that the equianalgesic dose ratio and equipotent ratio of two given opioids are the same. However, our results showed that the two ratios may be somewhat different. Whereas the equianalgesic dose ratio is a

clinical term, the equipotent ratio is a pharmacological term. Perhaps these two terms may be mistaken for the same concept. To the best of our knowledge, no study has simultaneously compared the equianalgesic concentration ratio and equipotent ratio of two opioids. Based on our current results, we suggest that the equianalgesic concentration ratio and the equipotent ratio are indeed distinct concepts under certain conditions.

Some issues may be considered as limitations of this study. First, the pharmacokinetic study was conducted on surgical patients and not in volunteers, which may be needed to rule out various factors that may affect the plasma concentration of fentanyl. Pharmacokinetic parameters may vary depending on factors such as concomitant medications, fluids, and bleeding during surgery; notably, one study reported differences in the pharmacokinetic parameters of propofol between patients and healthy volunteers.[29] However, no differences in pharmacokinetic parameters have been reported for opioids. There is a risk of muscle rigidity or respiratory depression when high doses of opioid are administered to conscious volunteers. In addition, no evidence has suggested that anesthetic drugs such as propofol, remifentanil, and rocuronium may directly affect the pharmacokinetics of fentanyl. Of course, these drugs may lower blood pressure and indirectly affect the pharmacokinetics of fentanyl, which has a high hepatic extraction ratio.[30] However, it is unlikely that the metabolic clearance of fentanyl was

reduced due to a decrease in hepatic blood flow in our study, because we ensured that blood pressure was well-maintained throughout the entire study. In Korea, fentanyl is most commonly used for postoperative pain control, so it may be appropriate to characterize the pharmacokinetics of fentanyl in surgical patients, as carried out in several previous studies.[2,14,31] Second, the sample size was somewhat small. In our previous population pharmacokinetics and analgesic potency studies on oxycodone, 54 and 50 surgical patients participated in the analysis, respectively.[14] In general, because population pharmacokinetic study is closer to exploratory study rather than confirmatory study, the sample size is determined by the number of subjects suitable for covariate exploration. It is generally accepted that a sample size of approximately 30 participants is appropriate, and due to the nature of the population analysis, the analysis can be performed on even fewer patients.[1,25,26,31]

## CONCLUSION

The time course of plasma fentanyl concentration was well-described by a three-compartment mammillary model using an allometric expression. The MEAC and analgesic potency of fentanyl in patients who underwent major intraabdominal open surgeries were 1 and 0.63 ng/ml, respectively. These results provide a scientific basis for the use of fentanyl for acute postoperative pain management in surgical patients. The equianalgesic concentration ratio and equipotent ratio of oxycodone to fentanyl were 75:1 and 100:1, respectively.

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**Table 1. Characteristics of the patient populations in the pharmacokinetic and analgesic-potency studies**

| | Pharmacokinetics study (n = 30) | Analgesic-potency study (n = 30) |
|---|---|---|
| ASA PS 1/2 | 9/21 | 7/23 |
| Age, yr | 53.5 ± 12.3 | 58 (50–62) |
| Weight, kg | 65.0 ± 10.2 | 62.8 ± 10.6 |
| Male/Female | 16/14 | 22/8 |
| Height, cm | 165.9 ± 7.8 | 163.2 ± 7.0 |
| BSA, $m^2$ | 1.7 ± 0.2 | 1.7 ± 0.2 |
| FFM, kg | 46.7 ± 9.3 | 47.0 ± 8.6 |
| IBW, kg | 60.4 ± 7.0 | 59.2 ± 6.1 |
| BMI, $kg/m^2$ | 23.6 ± 3.5 | 23.5 ± 3.0 |
| Operation, n (%) | | |
| BR | 9 (30.0) | – |
| ST | 11 (36.7) | 17 (56.7) |
| CRS | 4 (13.3) | 10 (33.3) |
| HBP | 6 (20.0) | 3 (10) |

Data are expressed as mean ± SD, median (25–75%), or count (%) as appropriate. ASA PS: American Society of Anesthesiologists Physical Status; BSA: body surface area (calculated using the Mosteller formula);[17] FFM: free fat mass (calculated using the Janmahasatian formula);[19] IBW: ideal body weight (calculated using the Robinson formula);[18] BMI: body mass index; BR: breast surgery including

transverse rectus abdominis myocutaneous flap; ST: stomach surgery including distal or total gastrectomy; CRS: colorectal surgery including right hemicolectomy, anterior resection, low anterior resection, and ileocecal resection; HBP: hepatobiliary surgery including pylorus-preserving pancreaticoduodenectomy.

**Table 2. Parameter estimates (RSE, % CV) of the competing basic and covariate pharmacokinetic models of fentanyl**

| | Model 1 | Model 2 | Model 3* | Model 4 | Model 5† |
|---|---|---|---|---|---|
| $V_1$, (l) | 42.2 (6.1, 13.3) | 9.89 (7.4, 25.8) | 2.34 (10.3, 33.5) | $3.47\times(WT/65)^{0.78}$ (26.4, 0.4) | $3.44\times(WT/65)^{0.786}$ (25.4, –) |
| $V_2$, (l) | – | 170 (4.7, 20.7) | 6.22 (11.0, 0.1) | $7.62\times(WT/65)^{0.78}$ (20.2, 0.3) | $7.59\times(WT/65)^{0.786}$ (15.4, –) |
| $V_3$, (l) | – | – | 141 (5.0, 20.5) | $152\times(WT/65)^{0.78}$ (6.1, 19.5) | $152\times(WT/65)^{0.786}$ (5.9, 19.5) |
| *Cl*, (l/min) | 0.315 (6.2, 11.8) | 0.803 (4.0, 19.3) | 0.71 (3.7, 18.2) | $0.745\times(WT/65)^{0.738}$ (4.2, 17.5) | $0.74\times(WT/65)^{0.737}$ (4.1, 17.6) |
| $Q_1$, (l/min) | – | 2.21 (6.7, 22.0) | 1.17 (10.8, 0.2) | $1.39\times(WT/65)^{0.738}$ (12.7, 1.3) | $1.38\times(WT/65)^{0.737}$ (10.8, –) |
| $Q_2$, (l/min) | – | – | 1.19 (6.8, 15.8) | $1.35\times(WT/65)^{0.738}$ (8.7, 22.4) | $1.35\times(WT/65)^{0.737}$ (9.0, 22.4) |
| OFV | 303.44 | –1125.06 | –1383.78 | –1398.87 | –1398.83 |
| Number of parameters (p) | 5 | 9 | 13 | 15 | 12 |
| AIC | 313.44 | –1107.06 | –1357.78 | –1368.87 | –1374.83 |

*selected basic model. †selected final model. OFV: objective function value (–2 log likelihood, –2LL); AIC: Akaike information criteria (–2LL + 2× p); CV: coefficient of variation; RSE: relative standard error = SE/estimate × 100 (%); WT: weight; Cl: metabolic clearance (l/min); $V_1$: central volume of distribution (l); $V_2$: rapid peripheral volume of distribution (l); $V_3$: slow peripheral volume of distribution (l); $Q_1$: inter-compartmental clearance of rapid peripheral compartment (l/min); $Q_2$: inter-compartmental clearance of slow peripheral compartment (l/min).

**Table 3. Population pharmacokinetic parameter estimates, inter-individual variability, and median parameter values (2.5–97.5%) of the non-parametric bootstrap replicates of the final pharmacokinetic model of fentanyl**

| Parameters | | Estimates (RSE, %) | CV (%) | Median (2.5–97.5%) |
|---|---|---|---|---|
| $V_1$ (L) = $\theta_1 \times (WT/65)^{\theta_7}$ | $\theta_1$ | 3.44 (25.4) | – | 3.50 (2.58–5.20) |
| $V_2$ (L) = $\theta_2 \times (WT/65)^{\theta_7}$ | $\theta_2$ | 7.59 (15.4) | – | 7.52 (6.06–11.6) |
| $V_3$ (L) = $\theta_3 \times (WT/65)^{\theta_7}$ | $\theta_3$ | 152 (5.9) | 19.5 | 153 (142–164) |
| $Cl$ (L/min) = $\theta_4 \times (WT/65)^{\theta_8}$ | $\theta_4$ | 0.74 (4.1) | 17.6 | 0.74 (0.70–0.78) |
| $Q_1$ (L/min) = $\theta_5 \times (WT/65)^{\theta_8}$ | $\theta_5$ | 1.38 (10.8) | – | 1.34 (1.16–1.54) |
| $Q_2$ (L/min) = $\theta_6 \times (WT/65)^{\theta_8}$ | $\theta_6$ | 1.35 (9.04) | 22.4 | 1.32 (1.18–1.47) |
| | $\theta_7$ | 0.786 (13.6) | – | 0.828 (0.198–1.310) |
| | $\theta_8$ | 0.737 (29.6) | – | 0.716 (0.001–1.080) |
| σ | | 0.0389 (10.3) | – | 0.0383 (0.0331–0.0432) |

A log-normal distribution of inter-individual random variability was assumed. Residual random variability was modeled using a constant coefficient of variation error model. Non-parametric bootstrap analysis was repeated 2000 times. RSE, relative standard error = SE/mean×100 (%). WT: weight.

**Figure 1. Plasma concentration of fentanyl over time (A) and goodness-of-fit plots of the final pharmacokinetic model of fentanyl in surgical patients (n = 30). (B) Population-predicted plasma concentration of fentanyl *vs.* measured plasma concentration of fentanyl. (C) Population-predicted plasma concentration of fentanyl *vs.* conditional weighted residuals (CWRES). (D) CWRES over time. Patients received an intravenous bolus of 100 μg fentanyl during operation. The brown dashed line indicates the line of identity.**

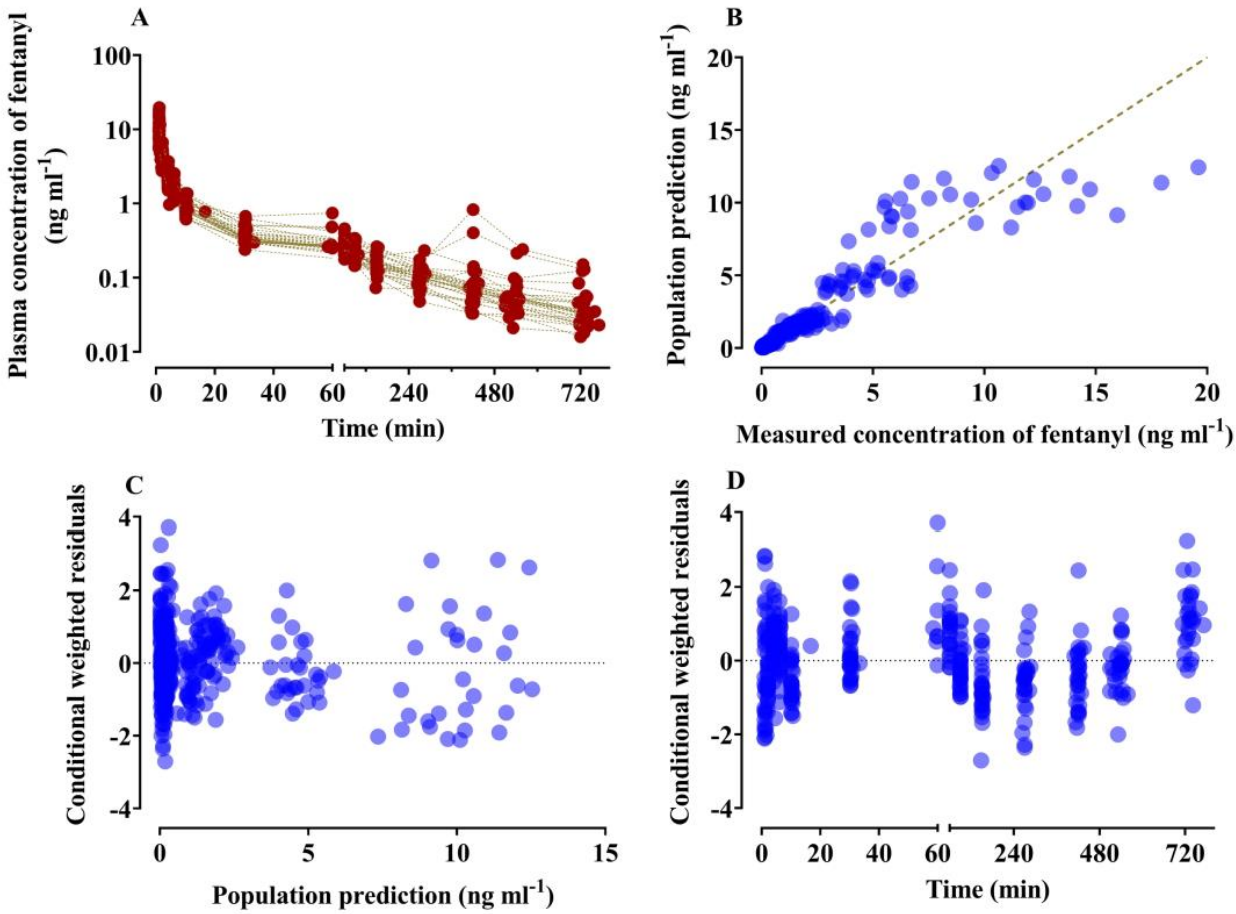


**Figure 2. Predictive checks of the final pharmacokinetic model of fentanyl. The solid red line and the solid blue line indicate the 50% prediction line and 90% prediction lines, respectively. The dotted green line indicates the 95% confidence lines of the 95% prediction lines. +: measured plasma concentration of fentanyl.**

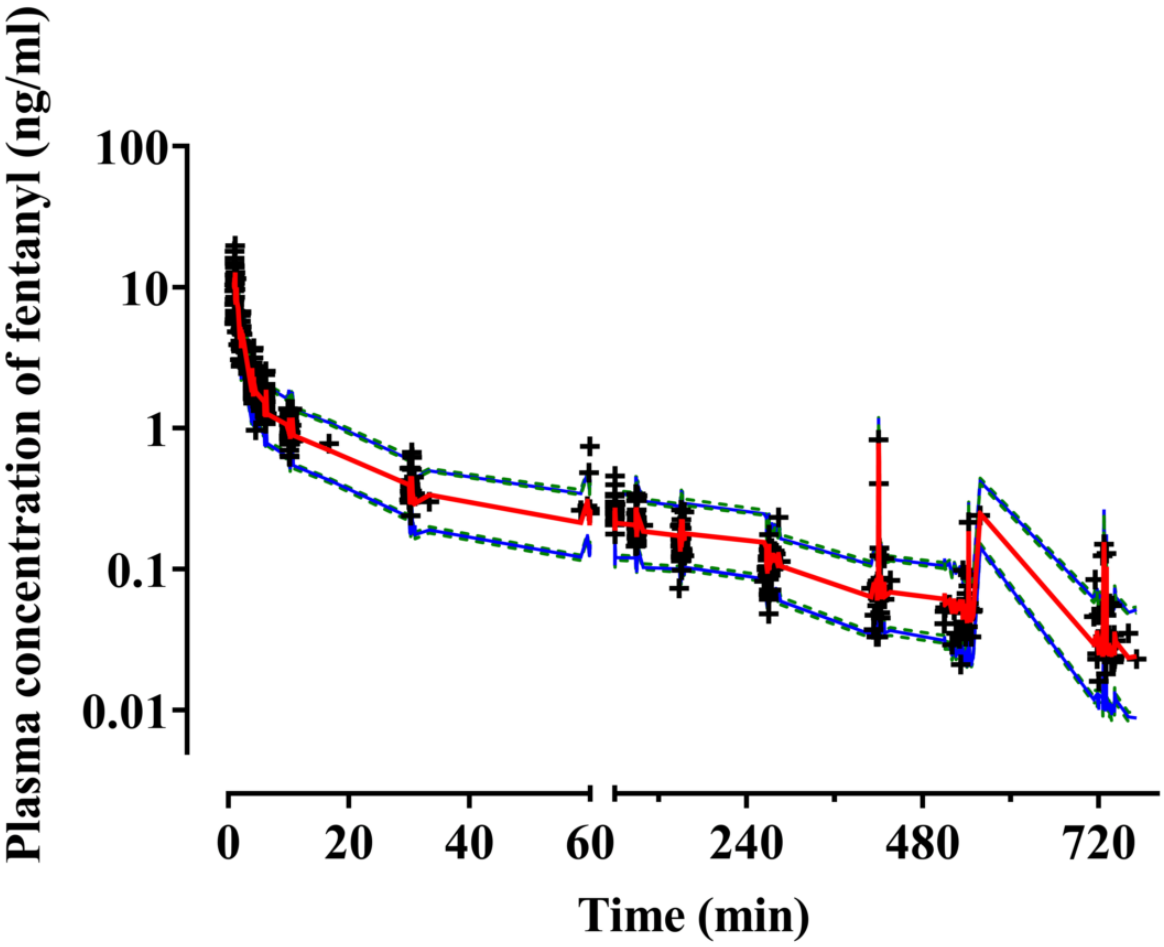


**Figure 3. Median values of the minimum effective concentration (MEC) and minimum effective analgesic concentration (MEAC) in the analgesic potency study. (A) Fentanyl, (B) Oxycodone (*from Choi BM, Lee YH, An SM, Lee SH, Lee EK, Noh GJ: Population pharmacokinetics and analgesic potency of oxycodone. Br J Clin Pharmacol 2017; 83:314-25*). Error bars indicate 5–95 percentiles. *: *P* < 0.05. Numbers within asterisks indicate the median MEC or MEAC. PACU: postanesthesia care unit.**

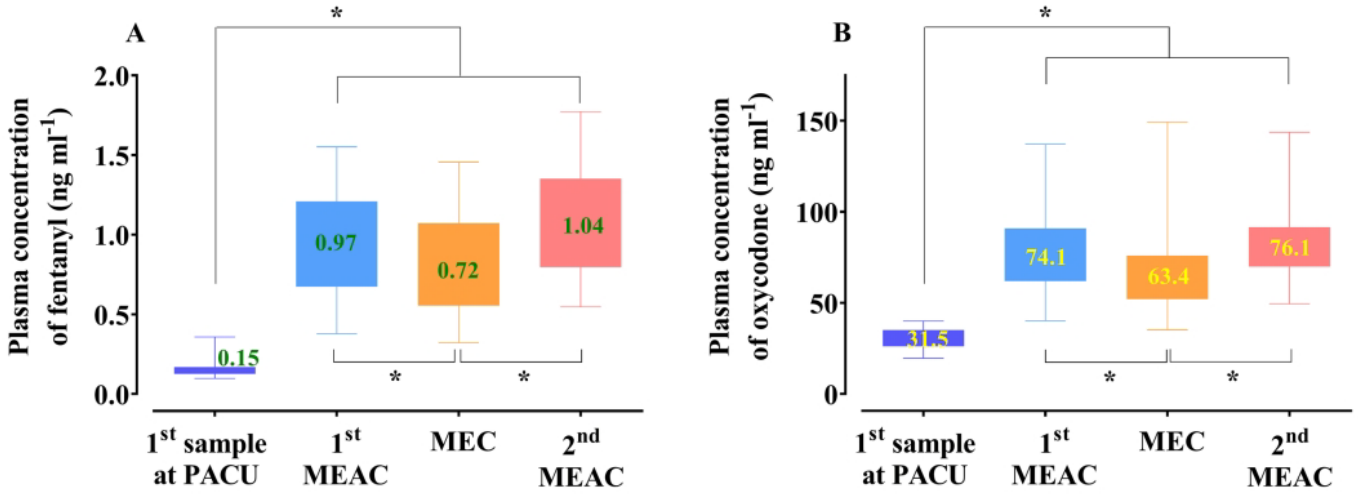


**Figure 4. Predicted probability for analgesia plotted against the plasma concentrations in the analgesic potency study. (A) Fentanyl, (B) Oxycodone. (*From Choi BM, Lee YH, An SM, Lee SH, Lee EK, Noh GJ: Population pharmacokinetics and analgesic potency of oxycodone. Br J Clin Pharmacol 2017; 83:314-25*). +: plasma concentration of fentanyl or oxycodone at minimum effective concentration (MEC), ×: plasma concentration of fentanyl or oxycodone at minimum effective analgesic concentration (MEAC). The solid red line indicates population prediction. The estimates of measured plasma fentanyl and oxycodone concentration associated with a 50% probability of analgesia ($Cp_{50}$) were 0.63 ng/ml and 59.9 ng/ml, respectively.**

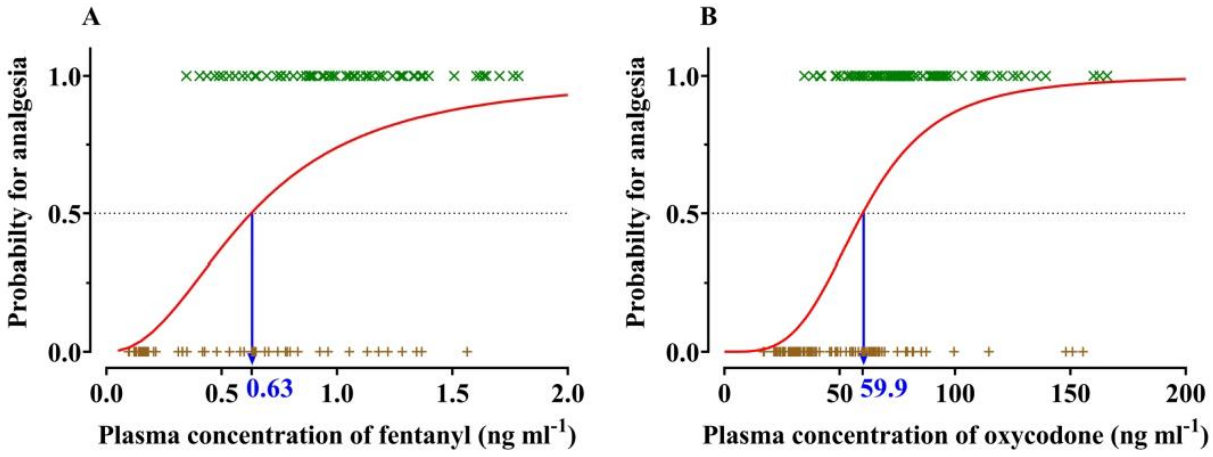
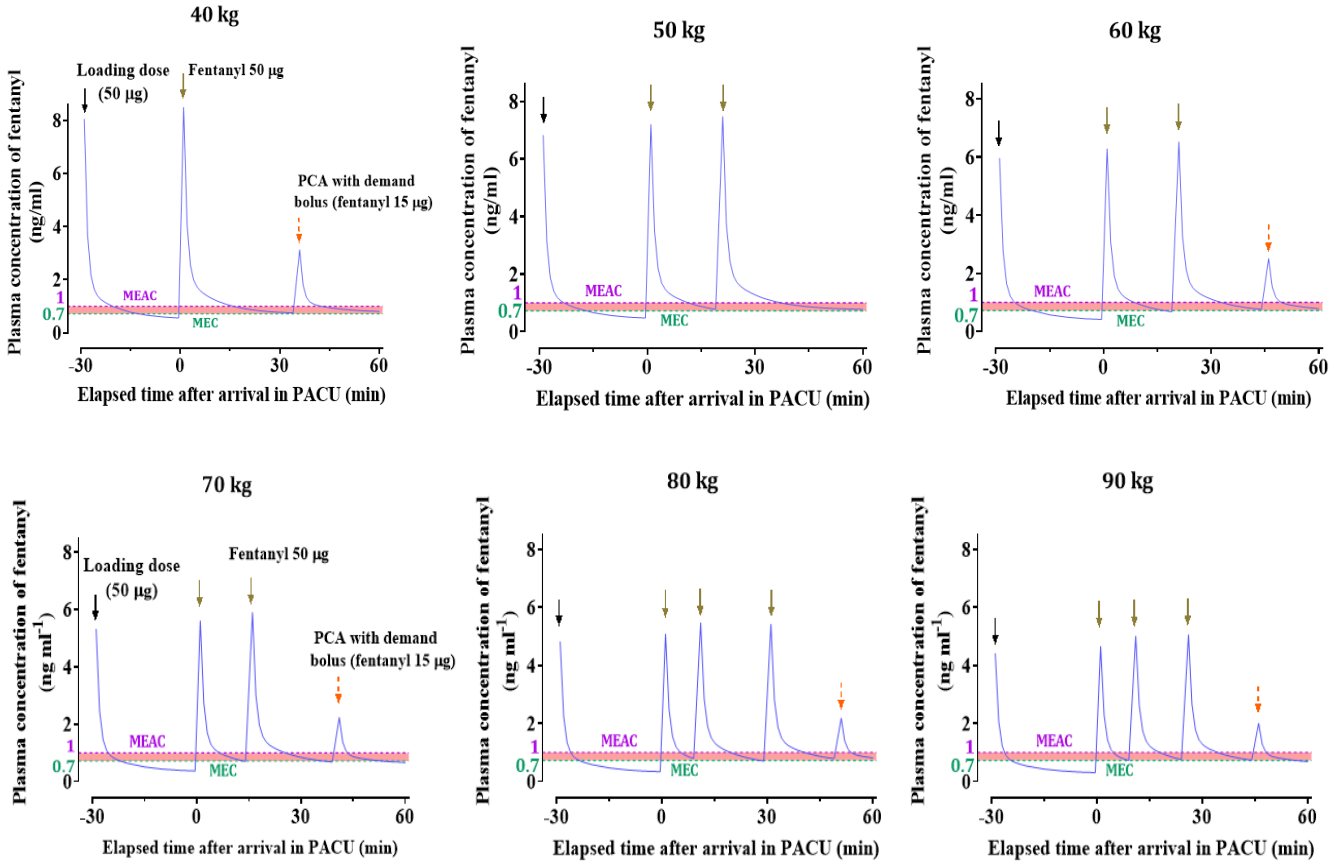


**Figure 5. Predicted concentration of fentanyl in the plasma over time after fentanyl administration for controlling postoperative pain in hypothetical patients weighing (A) 40 kg, (B) 50 kg, (C) 60 kg, (D) 70 kg, (E) 80 kg, or (F) 90 kg.**



# 국 문 요 약

**서론:** 정규 수술 환자들을 대상으로 펜타닐(fentanyl)의 집단 약동학을 분석하고 개복으로 주요 복부 수술을 받는 환자들을 대상으로 최소 유효 농도(MEC)와 최소 유효 진통 농도(MEAC)를 정하고자 하였다. 또한 이전 연구에서 얻은 옥시코돈(oxycodone)의 평균 MEAC 값을 이용하여 펜타닐과의 동등 진통 농도 비를 계산하고자 하였다.

**방법:** 약동약 분석 연구에서는 수술 중 펜타닐 100μg 을 정주하였고 정해진 간격으로 동맥혈을 채혈하였다. 진통 역가 분석 연구에서는 회복실에서 시행하였으며 시각 통증 척도(0= 통증 없음, 10=가장 극심한 통증)를 이용하여 10 분 간격으로 측정하였다. 안정 시 ≥ 3 이고 상처 압박 시 ≥ 5 면 첫번째 채혈을 하였다. 이후, 매 10 분마다 통증 정도를 측정하여 펜타닐 50 μg 을 정주하면서 안정 시< 3 이고 상처 압박 시 < 5 가 되면 두번째 채혈을 하고 이 지점을 펜타닐의 첫번째 MEAC 로 정하였다. 같은 과정을 반복하여 세번째 채혈로 MEC 와 4 번째 채혈로 두번째 2nd MEAC 를 정하고 분석하였다.

**결과:** 집단 약동한 연구 (n = 30)에서, 시간에 따른 펜타닐의 혈장내 농도는 상대 성장측정법을 이용해 삼구획 유선모형으로 잘 설명이 되었다. 진통 역가 연구 (n = 30)에서, MEC 의 중간 값은 0.72 ng/ml 였고, 첫번째와 두번째 측정한 MEAC 값은 각각 0.97 ng/ml and 1.04 ng/ml 로 나왔다.

**결론:** 이 연구의 결과로 수술 후 통증 조절을 위해 펜타닐을 사용할 때 과학적인 토대를 제공할 수 있다고 생각된다. 옥시코돈 대 펜타닐의 동등 진통 농도 비율과 동등 역가 비율은 각각 75:1 and 100:1 임을 알 수 있었다.

**중심단어**: 진통, 모델, 펜타닐, 약동학, 역가