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An allometric pharmacokinetic model and minimum effective analgesic concentration of fentanyl in patients undergoing major abdominal surgery

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Abstract

Background: We aimed to characterise the population pharmacokinetics of fentanyl in adults and to determine the minimum effective concentration (MEC) and minimum effective analgesic concentration (MEAC) of i.v. fentanyl in patients after major abdominal open surgery.
Methods: In the pharmacokinetic study, subjects received an intravenous bolus of fentanyl 100 μg during operation, and arterial blood was sampled at pre-set intervals. In addition, data from previously published fentanyl pharmacokinetic studies were incorporated to build a pharmacokinetic model. In the MEAC study, subjects were asked to rate their pain every 10 min using a VAS (0=no pain, 10=most severe pain) in the PACU. The first blood sample was obtained when wound pain was rated as ≥3 at rest or ≥5 during compression. Then, fentanyl 50 μg 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 first MEAC of fentanyl was measured. The same procedure was repeated to obtain a third sample (MEC) and a fourth sample (second MEAC).
Results: In the population pharmacokinetic study (n=95), the plasma concentration of fentanyl over time was well-described by the three-compartment mammillary model using an allometric expression. The V1, V2, V3, Cl, Q1, and Q2 of a 70 kg subject were 10.1, 26.5, 206 L, 0.704, 2.38, and 1.49 L min^{-1}, respectively. In the MEAC study (n=30), the median (inter-quartile range) MEC and MEAC were 0.72 (0.58–1.05) ng ml^{-1}, and 0.99 (0.76–1.28) ng ml^{-1}, respectively.
Conclusion: These results provide a scientific basis for the use of fentanyl for acute postoperative pain management in surgical patients.
Clinical trial registration: KCT0003273 (http://cris.nih.go.kr).

Keywords: effective; concentration; fentanyl; pain; pharmacodynamics; pharmacokinetics; postoperative pain

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Editor's key points

- Currently used fentanyl pharmacokinetic models were developed from studies in small numbers of subjects performed several decades ago.
- The authors studied the pharmacokinetics and dynamics of fentanyl in 30 patients undergoing abdominal surgery.
- They combined their pharmacokinetic data with those from 65 subjects enrolled in previously published studies and found that a three compartment mammillary model with allometric scaling best predicted the measured fentanyl concentrations.
- In the pharmacodynamic sub-study, the median minimum effective concentration and minimum effective analgesic fentanyl concentrations after surgery were 0.72 and 0.99 ng ml^{-1}, respectively.

Fentanyl is an opioid commonly used as an adjunct to general anaesthesia, the analgesic component of perioperative sedation, and for postoperative pain management. Over the past decades, many studies have been conducted on various populations to characterise the pharmacokinetics of fentanyl.[12] However, the number of subjects involved in each study was less than 20.[3–7] Therefore, a combined analysis of these studies may provide a clearer picture of the pharmacokinetics of fentanyl in adults.

Allometric scaling, a commonly used method in pharmacokinetic model development, provides an effective alternative option to interpolate or extrapolate pharmacokinetic parameters to a species of interest.[8] In general, when this technique is applied, the volume of distribution scales linearly with body weight and clearance with weight to the 0.75 power.[9] Indeed, the allometric remifentanil pharmacokinetic model developed by combining previously published data had better predictive performance than the individual models.[10]

The analgesic effect of fentanyl is closely related to its plasma concentrations at steady state; however, in the absence of a steady state, the concentration is more closely related to the effect-site concentrations.[11] The concepts of the minimum effective concentration (MEC, indicated by the need for i.v. rescue analgesics because of pain) and the minimum effective analgesic concentration (MEAC, indicated by the relief of pain by the administration of rescue analgesics) were used in many MEAC studies.[12–14] Therefore, maintaining fentanyl plasma or effect-site concentrations between MEC and MEAC 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.[121516] The MEAC of fentanyl was reported as 0.6–1 ng ml^{-1},[11] 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 combine several fentanyl pharmacokinetic datasets to develop an allometric pharmacokinetic model and to determine the MEC and MEAC of i.v. fentanyl for major abdominal open surgeries (e.g. gastric, colorectal, and hepatobiliary surgeries). In addition, we calculated the MEAC ratio of oxycodone to fentanyl by comparing the median MEAC value of oxycodone, which was described in our previous similarly-designed study on oxycodone.[14]

Methods

Patient population

This study was approved by the Institutional Review Board of 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: B.-M.C., date of registration: October 18, 2018) before the enrolment of the first subject. The study consisted of two clinical trials—a population pharmacokinetic study (n=30) and an MEAC study (n=30). Written informed consent was obtained from all participating subjects. The subjects were enrolled in the pharmacokinetic and MEAC studies during November 2018 to February 2019 and November 2018 to December 2018, respectively. Inclusion criteria were age between 20 and 80 yr and ASA physical status 1 and 2. Exclusion criteria were as follows: history of allergic response to fentanyl, long-term use of opioid medications, haemoglobin concentration < 9 g dl^{-1}, pregnancy, history of hepatic, cardiopulmonary, or renal disease, or history of chronic pain. The patient groups in the MEAC study consisted of surgical patients who were undergoing elective stomach, colorectal, or hepatobiliary surgery. Patients undergoing laparoscopic surgery were excluded from the MEAC study.

Procedures for pharmacokinetic and MEAC studies

All subjects fasted for 6–8 h before surgery without premedication. In the operating theatre, all patients were monitored with ECG, pulse oximetry, noninvasive BP, train-of-four, end-tidal carbon dioxide partial pressure (Carescape B850; GE Healthcare, Milwaukee, WI, USA), and the bispectral index (BIS monitor; Covidien, Boulder, Colorado, USA). Anaesthesia was induced and maintained with target effect-site concentration-controlled infusion of propofol and remifentanil (Perfusor® Space; B. Braun Melsungen AG, Melsungen, Germany).[1718] Tracheal intubation was performed after administration of rocuronium 0.6 mg kg^{-1}. A 20-G 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 haemodynamics (systolic BP>80 mm Hg; HR>45 beats min^{-1}), respectively. I.V. patient-controlled analgesia (i.v. 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^{-1}, and lock-out time of 15 min. The concentration of oxycodone in i.v. PCA bag was 1 mg ml^{-1}, and 200 ml of oxycodone-normal saline mixture was delivered to patients over 3–4 days. In the MEAC study, the oxycodone PCA device was connected to the patient after the last blood collection.

Intervention for the pharmacokinetic study

Subjects received a single i.v. bolus of fentanyl citrate 100 μg (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. In addition, previously published fentanyl pharmacokinetic data were incorporated to build an

Table 1 Details of the datasets included in the pharmacokinetic (PK) and minimum effective analgesic concentration (PD) studies.

Dataset	N	Observations		Study group	Age, yr	Weight, kg	Reference	Source
		PK	PD					
McClain and Hug	7	154	–	Volunteers	22–29	65.0–84.5	3	Steven L. Shafer
Scott and Stanski	19	593	–	Patients	20–88	62.7–105.0	4	Steven L. Shafer
Hudson and colleagues	10	204	–	Patients	55–80	59.1–103	5	Steven L. Shafer
Varvel and colleagues	8	150	–	Patients	33–57	52.3–100	6	Steven L. Shafer
Shafer and colleagues	21	604	–	Patients	58 (11)	40.0–100	7	Steven L. Shafer
Choi and colleagues (current study)	30	387	–	Patients	32–73	46.4–84.5	–	–
Choi and colleagues (current study)	30	–	120	Patients	33–73	42.3–92.4	–	–

Data are presented count, range, or mean (SD) as appropriate. Dr. Steven L. Shafer provided previously published pharmacokinetic data.

allometric pharmacokinetic model. Details of the component datasets are summarised in Table 1.

Intervention for the MEAC study

Subjects received fentanyl (1 μg kg^{-1}) 30 min before the end of surgery. After the end of surgery, tracheal extubation was performed when the train-of-four ratio was greater than 0.9 and the BIS value was greater than 80. Patients were transported to the PACU, where their state of consciousness was assessed with a modified Aldrete score.[19] ECG, pulse oximetry, and noninvasive BP were also monitored. Thereafter, the patients were assessed for pain every 10 min using a 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 i.v. fentanyl 50 μg 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.[12] 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.[12] The subjects were then administered with i.v. fentanyl 50 μg 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. Medications that could affect pain perception (e.g. NSAID) were not administered during surgery or in the PACU.

Blood sample acquisition and assay

Blood samples were collected in ethylenediaminetetraacetic acid-containing tubes and centrifuged for 10 min at 1500×g. The plasma was stored at −70°C until used for assay. A total of 100 μl of plasma was used for assay. Protein precipitation was used in plasma sample preparation for liquid chromatography–mass spectrometry (LC-MS)/MS analysis. After adding internal standard 10 μl (donepezil 100 ng ml^{-1}) and acetonitrile 300 μl to plasma 100 μl, the mixture was vortexed for 1 min. After centrifugation at 9185×g for 5 min, the supernatant was transferred to a polypropylene vial, of which 2 μl was directly injected into the LC-MS/MS system. Plasma concentrations of fentanyl were analysed using an ultrafast liquid chromatography system (Shimadzu, Kyoto, Japan) coupled with tandem MS (API5500; SCIEX, Framingham, MA, USA). A Luna phenyl-hexyl column (Phenomenex, Torrance, CA, USA) was used for chromatographic separation. The dimensions of the analytical column were 100×2 mm and the column particle size was 3 μm. The mobile phase consisted of a mixture of ammonium formate 10 mM (with formic acid 0.1%) in water and acetonitrile (50:50, v/v), and a flow rate of 0.3 ml min^{-1} was used. The column oven temperature was maintained at 40°C, 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. Donepezil was used as an internal standard. The validated quantification range was 0.01–20 ng ml^{-1}. The lower limit of quantification (LLoQ) was 0.01 ng ml^{-1}. The coefficient of variation (CV) at the assay LLoQ was 10%. 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 % CV, were <11.1% and <10.0%, respectively.

Population pharmacokinetic analysis

The population pharmacokinetic analysis was performed with NONMEM VII level 4 (ICON Development Solutions, Dublin, Ireland). One-, two-, and three-compartment mammillary models using the ADVAN13 subroutines and first-order conditional estimation with interaction were fitted to the fentanyl concentrations. A log-normal model was used to estimate the interindividual random variability of pharmacokinetic parameters. Covariance between parameters was assessed using an omega block. Constant CV residual error model was applied to the model building. The NONMEM computed the minimum objective function value, a statistical equivalent to the −2 log-likelihood of the model. An α level of 0.05, which corresponded to a reduction in the objective function value of 3.84 (χ^2 distribution, degrees of freedom=1, $P<0.05$), was used to distinguish between hierarchical models.[20] The fit of the data was also tested by allometric expression.[10] 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).[21] Log-likelihood profiling was used to calculate the confidence interval for the estimated parameters (PDx-Pop 5.2, ICON Development Solutions, Dublin, Ireland).[22]

The posterior predictive performance was visually evaluated using fit4NM 3.3.3.[23] Median prediction error (MDPE, bias) and median absolute prediction error (MDAPE, inaccuracy) were calculated to evaluate the predicted performance of the newly developed pharmacokinetic model.[24] Methods for calculating these parameters were described in detail in our previous study.[25] In the MEAC study, the effect-site concentration (*Ce*) was calculated to collapse the hysteresis between the time course of fentanyl concentration in the plasma and the time course of the effect of fentanyl. To calculate the *Ce*, we used the value (0.147 min^{-1}) of the blood-brain equilibrium rate constant (k_{e0}) obtained in a study on the development of a pharmacokinetic model.[4]

Determination of analgesic potency using logistic regression

To determine the analgesic potency, pain was defined as the need for additional fentanyl administration. No pain was defined as situations in which rescue fentanyl was not required. Every measured plasma fentanyl concentration was joined to 0 (pain, first and third samples) or 1 (no pain, second and fourth samples). The relationship between the probability of analgesia and the measured plasma fentanyl concentration was analysed using a sigmoid E_{max} model [equation (1)]:

$$\text{Probability of analgesia} = \frac{C_p^{\gamma}}{C_{p50}^{\gamma} + C_p^{\gamma}} \quad (1)$$

where C_p is the measured plasma fentanyl concentration, C_{p50} is the plasma concentration associated with a 50% probability of analgesia, and γ is the steepness of the concentration *vs* response relation. The likelihood of the observed response (R) was described by equation (2):

$$\text{Likelihood} = R \times \text{Prob} + (1 - R) \times (1 - \text{Prob}) \quad (2)$$

where Prob is the probability of analgesia. Model parameters were estimated using the option 'LIKELIHOOD LAPLACE METHOD=conditional' in the NONMEM. The interindividual variabilities of C_{p50} and γ were modelled using a log-normal model.

Simulation

Based on the MEC and MEAC measured from the MEAC 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 intraindividual random variability were performed using a simulation program (Asan Pump, version 2.1.3; Bionet Co., Ltd, Seoul, Korea).

MEAC ratio of oxycodone to fentanyl

To obtain the MEAC ratio of oxycodone to fentanyl, the results of oxycodone from a previous study were used.[14] In the same design as the current fentanyl study, the study on population pharmacokinetics and MEAC of oxycodone was conducted in a similar manner with a previous study.[14] The MEAC study design of oxycodone was identical except that the doses of oxycodone administered as rescue analgesics in the PACU were different. Patients received i.v. oxycodone 2 mg (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 MEAC ratio was calculated by comparing the median MEACs of fentanyl and oxycodone in each study.

Statistical analysis

Statistical analysis was conducted using the SigmaStat software version 3.5 for Windows (Systat Software, Inc., Chicago, IL, USA). The four concentrations (first sample, second sample [first MEAC], third sample [MEC], fourth sample [second MEAC]) obtained in the MEAC 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 mean (standard deviation) for normally distributed continuous variables, median (25–75%) for non-normally distributed continuous variables, and counts and percentages for categorical variables.

Results

Population pharmacokinetics of fentanyl

In total, 2095 blood samples were obtained from 95 subjects. Three of these samples were excluded from the analysis because of an overly high fentanyl concentration (514.1 ng ml^{-1}) at 10 min after a single i.v. bolus of fentanyl 100 μg in one subject (ID90) and low fentanyl concentrations below the LLoQ in two subjects (ID71 and ID94). Hence, 2092 plasma concentration measurements were used to characterise the pharmacokinetics of fentanyl. In two subjects (ID80 and ID86), fentanyl was inadvertently administered in the PACU for pain control and an elevation of concentration was observed around 420 min. These two subjects were included in the pharmacokinetic analysis. In all other subjects, exponential decreases in fentanyl concentration over time were observed.

The three-compartment model best described the pharmacokinetics of fentanyl in surgical patients. The final NONMEM control stream and the related data file are presented in Supplementary material. The parameter estimates of the competing base and covariate pharmacokinetic models of fentanyl are described in Supplementary material (Supplementary Table S1). The model that applied the allometric expression was selected as the final model. Table 2 shows the population pharmacokinetic parameter estimates and the results of non-parametric bootstrap replicates of the final pharmacokinetic model of fentanyl. The frequency distributions of the parameters estimated by the bootstrap validation are presented in Supplementary Figure S1. The population model (Fig 1a) estimated the measured fentanyl concentration with reasonable accuracy (MDPE: −2.1%, MDAPE: 22.7%). The individual *post hoc* model (Fig 1b) did not show evidence of model misspecification (MDPE: 1.2%, MDAPE: 8.3%). Goodness-of-fit plots of the final pharmacokinetic model of fentanyl are presented in Fig 1c and d. Overall, the data were distributed around the line of identity. Posterior predictive performance plots of each of the final pharmacokinetic models

Table 2 Population pharmacokinetic parameter estimates, interindividual 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 (%)	CI	Median (2.5–97.5%)
V_1 (L)=$\theta_1\times(WT/70)^{\theta7}$	θ_1	10.1 (8.8)	67.5	8.7–11.8	9.6 (8.6–10.6)
V_2 (L)=$\theta_2\times(WT/70)^{\theta7}$	θ_2	26.5 (14.2)	71.6	22.0–31.6	25.3 (22.1–29.2)
V_3 (L)=$\theta_3\times(WT/70)^{\theta7}$	θ_3	206 (5.6)	36.7	188–227	201 (189–215)
Cl (L min^{-1})=$\theta_4\times(WT/70)^{\theta8}$	θ_4	0.704 (3.4)	30.8	0.657–0.752	0.718 (0.682–0.753)
Q_1 (L min^{-1})=$\theta_5\times(WT/70)^{\theta8}$	θ_5	2.38 (7.4)	67.2	2.05–2.77	2.24 (2.03–2.47)
Q_2 (L min^{-1})=$\theta_6\times(WT/70)^{\theta8}$	θ_6	1.49 (5.8)	49.4	1.33–1.67	1.42 (1.31–1.54)
	θ_7	1.23 (17.8)	–	0.87–1.61	1.18 (0.81–1.51)
	θ_8	0.313 (45.4)	–	0.037–0.583	0.387 (0.158–0.618)
σ	0.0262 (9.0)		–	–	0.0275 (0.0241–0.0307)

A log-normal distribution of inter-individual random variability was assumed. Residual random variability was modelled using a constant coefficient of variation (CV) error model. Non-parametric bootstrap analysis was repeated 2000 times.
CI, confidence interval calculated by log-likelihood profiling; RSE, relative standard error=SE mean$^{-1}\times100$ (%); WT, weight.

for fentanyl are presented in Fig 2. In total, 7.5% of the data (a: 2.6%, b: 9.3%, c: 3.9%, d: 6.0%, e: 10.4%, f: 4.4%) were distributed outside of the 90% prediction intervals, 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 fentanyl of 250 (100–350) μg and 50 (50–100) μg were required to achieve the first and second MEAC, respectively. A total of 120 plasma concentration measurements from 30 subjects were used to determine the MEC and MEAC

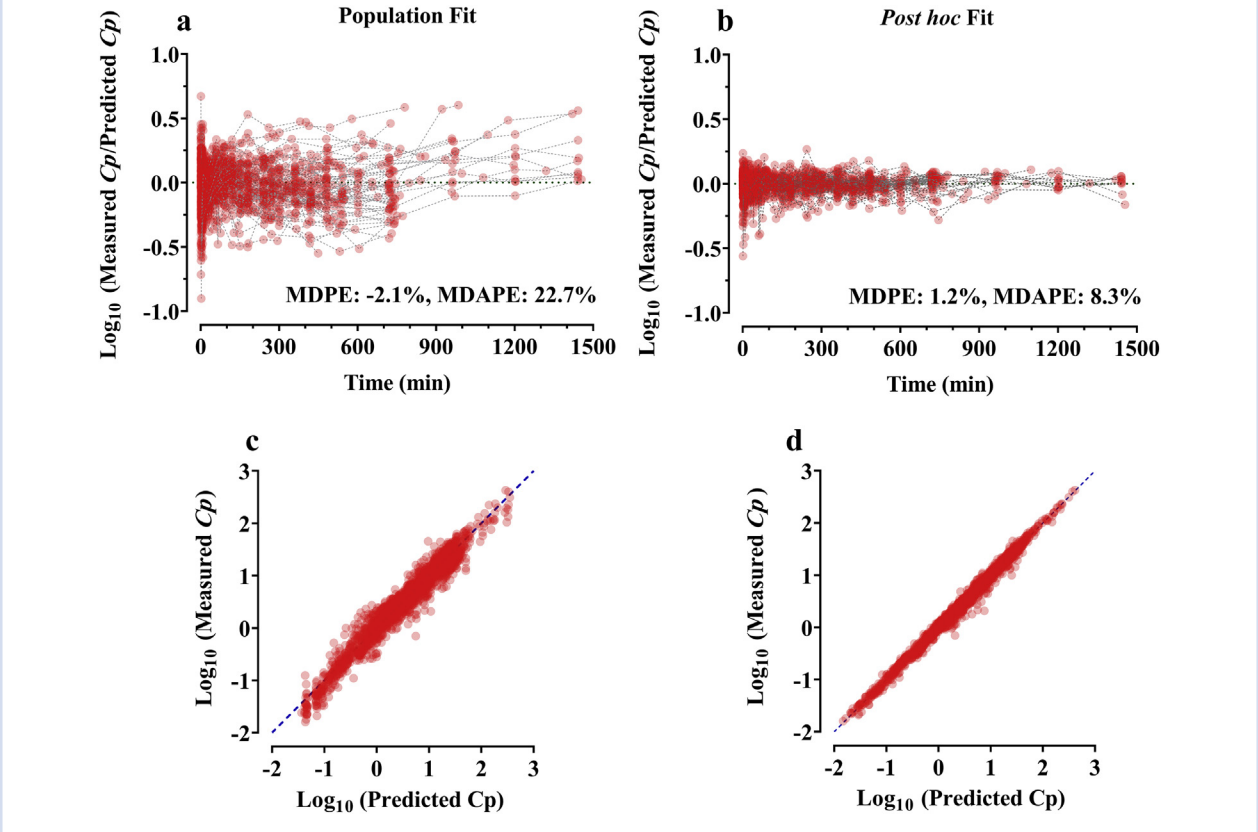

Figure 1. Panels (a) and (b) present the log of the ratio of the observed *vs* predicted plasma concentration of fentanyl (C_p) for the population (A) and the individual *post hoc* (B) model fits as a function of time. Performance metrics of the respective models (median prediction error [MDPE] and median absolute prediction error [MDAPE]) are also shown. Panels (c) and (d) show the goodness-of-fit for the population prediction (C) and the prediction based on the individual *post hoc* estimates *vs* the observed C_p. The blue dotted lines indicate the line of identity.

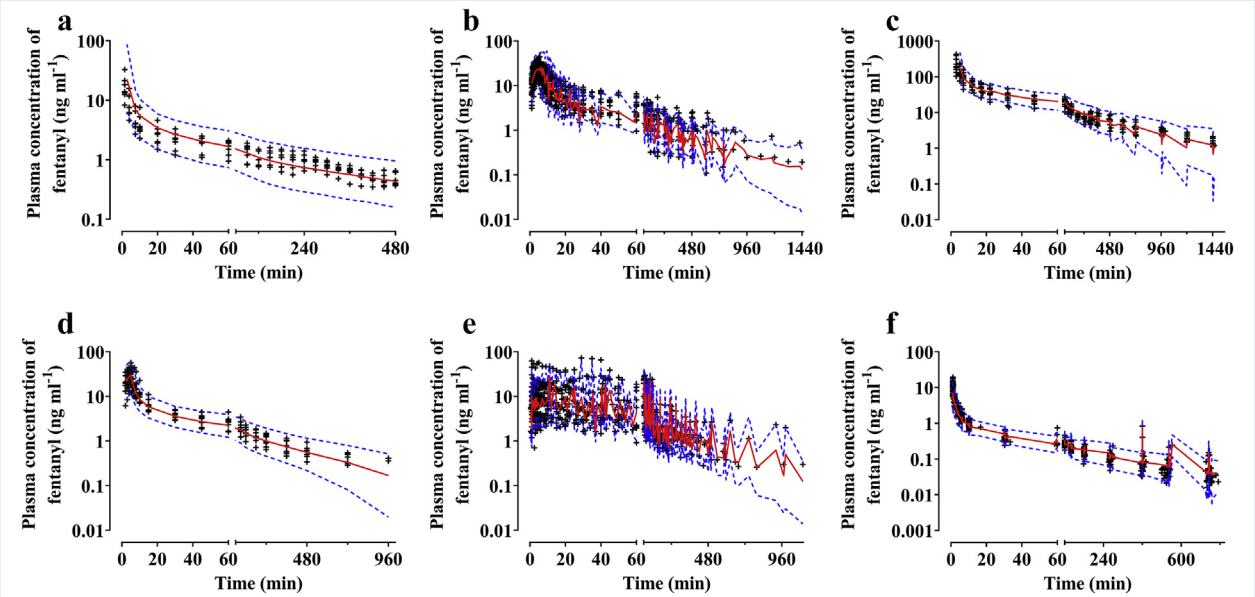

Figure 2. Visual evaluation of the posterior predictive performance of each of the final pharmacokinetic models for fentanyl. Study by (a) McClain and Hug[3] (n=7), (b) Scott and Stanski[4] (n=19), (c) Hudson and colleagues[5] (n=10), (d) Varvel and colleagues[6] (n=8), (e) Shafer and colleagues[7] (n=21), and (f) Choi and colleagues (current study, n=30). The solid red line and the solid blue line indicate the 50% prediction line and 90% prediction lines, respectively. +, measured plasma concentration of fentanyl.

and to perform the logistic regression analysis. When the 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^{-1}. The median (25–75%) plasma concentration of fentanyl at the second blood sample (MEC) was 0.72 (0.58–1.05) ng ml^{-1}. The median (25–75%) effect-site concentration corresponding to the MEC time point was 1.09 (0.72–1.57) ng ml^{-1}. At the first and second pain relief (first MEAC and second MEAC), the median plasma concentrations of fentanyl were 0.97 (0.70–1.20) ng ml^{-1} and 1.04 (0.81–1.34) ng ml^{-1}, respectively (Fig 3a). Across the MEAC time points, the median (range) plasma concentration of fentanyl was 0.99 (0.35–1.79) ng ml^{-1}. The median (25–75%) effect-site concentration corresponding to the MEAC time point was 1.73 (1.44–2.55) ng ml^{-1}. The simulated plasma and effect-site concentrations of fentanyl administered in a patient (ID3) in the MEAC study are shown in Supplementary Figure S2. The estimates of C_{p50} (standard error) and γ (standard error) estimated by logistic regression were 0.63 (0.05) ng ml^{-1} and 2.24 (0.24), respectively (Supplementary Figure S3). The η estimates for both parameters were too small (C_{p50}: 9.75E−15, γ: 4.33E−15) to fix the η to zero.

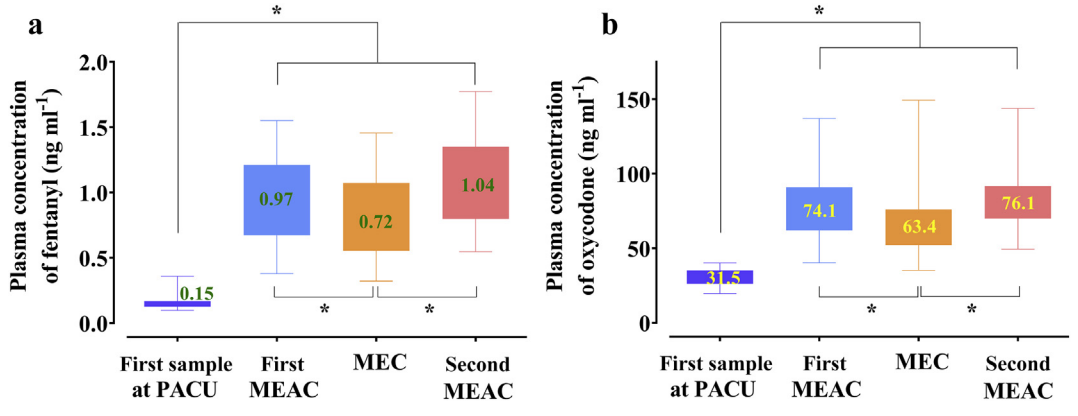

Figure 3. Median values of the minimum effective concentration (MEC) and minimum effective analgesic concentration (MEAC). (a) Fentanyl, (b) oxycodone.[14] Error bars indicate 5–95 percentiles. *P<0.05. Numbers within asterisks indicate the median MEC or MEAC.

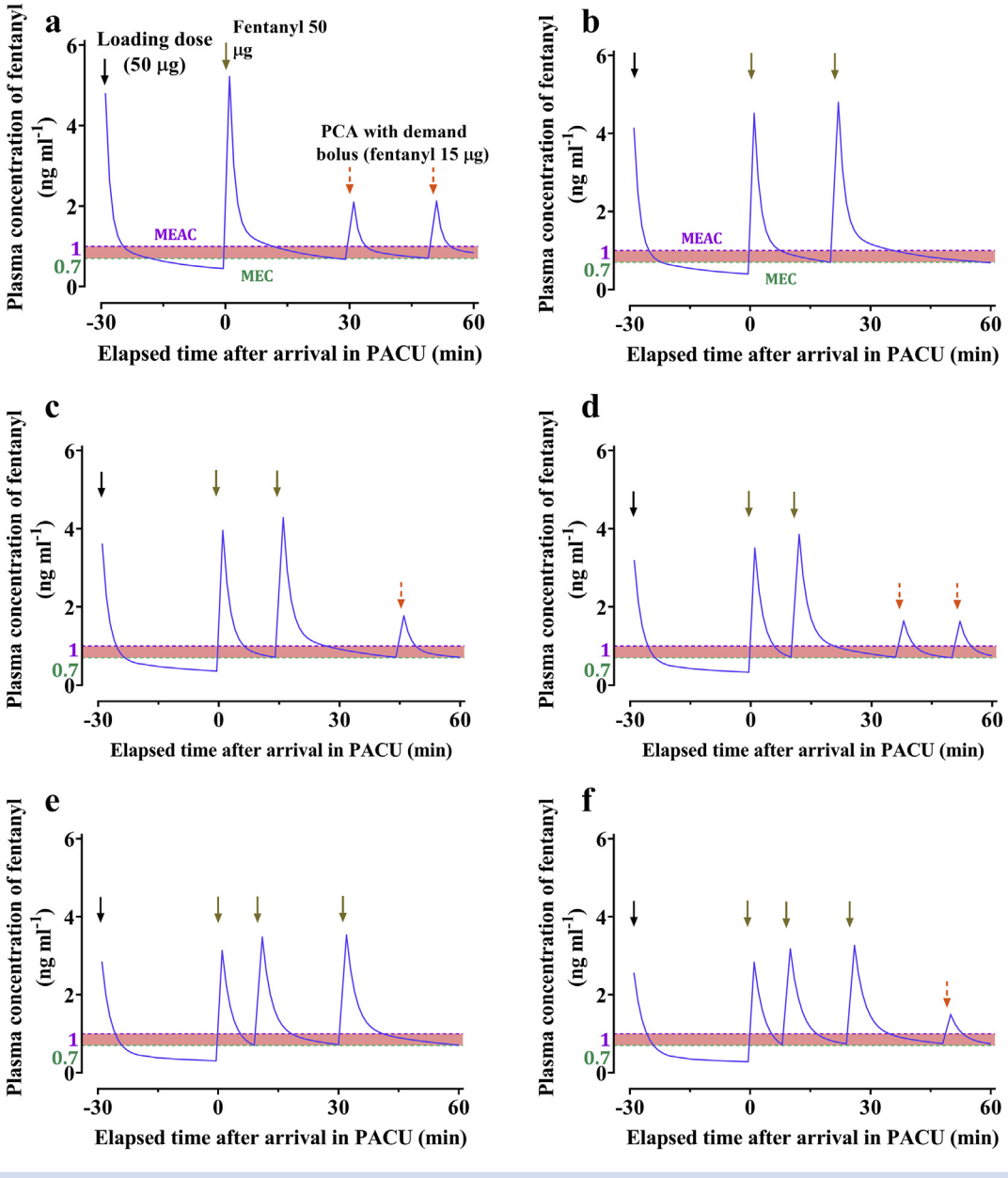

Figure 4. Predicted concentration of fentanyl in the plasma over time after fentanyl administration for controlling postoperative pain in hypothetical patients weighing (a) 40 kg, (b) 50 kg, (c) 60 kg, (d) 70 kg, (e) 80 kg, or (f) 90 kg. It was assumed that fentanyl 50 μg was administered as a loading dose 30 min before arrival in the PACU. The basal rate of patient-controlled analgesia (PCA) was set to 15 μg h^{-1}.

Simulation

The fentanyl dosing regimens for managing postoperative pain in the PACU were described for hypothetical patients with varying weights (Fig 4). Fentanyl 50 μg was administered 30 min before transfer to the PACU, and the demand bolus of i.v. PCA was assumed to be 15 μg. The basal rate of PCA was set to 15 μg h^{-1}. It was also assumed that the patient stayed in the PACU for approximately 1 h. For patients weighing < 50 kg, one dose of 50 μg fentanyl was administered as a rescue analgesic in the PACU, and the demand bolus was given twice before the patient went to the general ward. For patients weighing > 50 kg and less than 80 kg, two doses of fentanyl 50 μg were required in the PACU. For patients weighing more than 80 kg, three doses of fentanyl 50 μg were administered to maintain the plasma concentrations of fentanyl at above the MEC.

MEAC ratio of oxycodone to fentanyl

In the previous study, the first and second median (25–75%) MEACs of oxycodone were 74.1 (62.3–90.0) ng ml^{-1} and 76.1 (70.9–91.4) ng ml^{-1}, respectively (Fig 3b).[14] Based on the results

of the previous and current studies, the MEAC ratio of oxycodone to fentanyl was 75:1.

Discussion

Changes in plasma concentrations of fentanyl over time 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^{-1}, respectively. The MEAC ratio of oxycodone to fentanyl was 75:1.

The interindividual variability of pharmacokinetic parameters is commonly described by body size including weight.[1726] 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.[10] Traditionally, the allometric exponents of volumes and clearances had been fixed at 1 and 0.75[10]; however, estimating these allometric exponents sometimes even further reduced the objective function value.[27] 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 (see Supplementary Table S1). Also, the MDAPE value of the final model was slightly smaller than that of the standard allometric model (standard allometric model: 23.7%, final model: 22.7%). Indeed, it is better to choose a parsimonious model if it shows a similar performance; however, adding two parameters resulted in a decrease in the objective function value by 12.61, which was statistically significant (P=0.002). Thus, the model that estimates the exponents of the volume and clearance was chosen as the final model instead of the standard allometry method. Some studies described the interindividual variability of fentanyl pharmacokinetic parameters according to body weight.[1,7] 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. Aging induces changes in the body composition and deteriorates the renal function, which can affect the pharmacokinetics of a drug. Several studies have investigated whether age is a potential factor influencing the pharmacokinetics of fentanyl[28–30]; however, because of variations in methods and pharmacokinetic parameters, solid conclusions could not be drawn.[1]

In the MEAC study, the fentanyl plasma concentration of the third blood sample (MEC) was about six times higher than that of the first 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 first and third blood sample concentrations in the PACU as the first and second MECs.[1214] The first blood sample concentration is not the first MEC; rather, any concentration below the MEC and the third blood sample is the actual first MEC. Therefore, we corrected the figure from a previous oxycodone study and presented it in Fig 3b. Considering that the two measured MEAC values were similar, the MEAC could be considered reliable. The MEAC values of fentanyl determined in our study fall within the range of MEAC (0.6–1.0 ng ml^{-1}) reported in a previous study.[11] In that previous study,[11] 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^{-1} 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^{-1}. 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.

MEC and MEAC are known to show differences depending on the type of surgery.[121415] In the current MEAC study on fentanyl, patients undergoing major open abdominal surgery were enrolled and divided into three surgical groups (ST: stomach surgery [n=17], CRS: colorectal surgery [n=10], HBP: hepatobiliary surgery [n=3]). MEC and MEAC did not show significant differences among the groups. (MEC: 0.78 [0.35] ng ml^{-1} for ST, 0.77 [0.35] ng ml^{-1} for CRS, and 0.96 [0.42] ng ml^{-1} for HBP, P=0.682, one-way ANOVA, MEAC: 1.01 (0.36) ng ml^{-1} for ST, 0.98 (0.38) ng ml^{-1} for CRS, and 1.18 (0.42) ng ml^{-1} for HBP, P=0.517). In previous studies on the MEC of fentanyl, the range of MEC was 0.23–0.99 ng ml^{-1} in Woodhouse and Mather[31] and 0.2–8.0 ng ml^{-1} in Lehmann and colleagues,[32] which were somewhat different from the results of the current study (0.31–1.56 ng ml^{-1}). This difference may as a result of the differences in the method for evaluating MEC and the type of surgery.

The potency ratio is a measure of the relative potency of two drugs and is defined as the ratio between equi-effective doses of two drugs. Many studies evaluated the potency ratio of oxycodone and fentanyl and reported somewhat varying results.[33–36] In most studies including these studies, the potency ratios were calculated using doses that showed the same effect. However, calculating the potency ratio by doses can be somewhat flawed because of the pharmacokinetic differences. Doses that are equally effective 10 min after administration may be completely skewed in either direction at 20 min because the pharmacokinetic curves are not identical. Therefore, the MEAC ratio may be a much more useful concept than the potency ratio. In a previous study, the MEAC ratio of sufentanil to fentanyl was reported as 1:15.[37]

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.[38] There is a risk of muscle rigidity or respiratory depression when high doses of opioid are administered in conscious volunteers. According to Bouillon and colleagues,[39] coadministration of propofol decreased the central volume of distribution and distributional clearance of remifentanil by 41% and elimination clearance by 15%. Based on the results of this study, it is possible that propofol may have influenced the pharmacokinetics of fentanyl. However, no evidence has suggested that anaesthetic drugs such as propofol, remifentanil, and rocuronium directly affect the pharmacokinetics of fentanyl. Of course, these drugs may lower BP and indirectly affect the pharmacokinetics of fentanyl, which has a high hepatic extraction ratio.[40] However, it is unlikely that the metabolic clearance of fentanyl was reduced as a result of a decrease in hepatic blood flow in our study, because we ensured that BP

was well maintained throughout the entire study. In Korea, fentanyl is most commonly used for postoperative pain control, so it may be appropriate to characterise the pharmacokinetics of fentanyl in surgical patients, as carried out in several previous studies.[114] Second, fentanyl was administered in a single bolus injection instead of continuous infusion. In general, when constructing a pharmacokinetic model, it is common to choose zero-order infusion.[3–6] Single bolus injection assumes instantaneous mixing as soon as the drug is injected, but there is actually a transit delay. A pharmacokinetic study with samplings during and after the continuous infusion has fewer oscillations and offsets the model's misspecification with increasing and decreasing concentrations. However, fentanyl is usually administered to patients as a single bolus injection rather than a continuous infusion. Therefore, in this study, we chose the administration method that is mainly used in clinical practice. Single bolus injections were also used in previous studies that developed pharmacokinetic models for fentanyl.[2841] Third, the k_{e0} obtained from a previous study was used to calculate the *Ce*. The *Ce* is required to collapse the hysteresis between the time course of the drug concentration in the plasma and the time course of the drug effect, and the *Ce* is calculated using k_{e0}. The k_{e0} can be estimated in two ways: the standard method is using an integrated pharmacokinetic/pharmacodynamics modelling technique in a single population. However, the k_{e0} could not be obtained in this manner because only the pharmacokinetic modelling was performed in the current study. The MEAC study was conducted in another population that was not involved in the construction of the pharmacokinetic model. The other way is using a model independent of the time-to-peak effect (t_{peak}) to estimate the k_{e0}. Because the t_{peak} is the time at which *Ce* reaches its maximal value, the derivative of *Ce* with respect to *t* should be zero at $t=t_{peak}$. In the current study, the time-to-peak effect was not observed. So, inevitably, k_{e0} obtained from another article was used. To calculate the *Ce*, we used the value (0.147 min^{-1}) of the k_{e0} obtained from a study on the development of a pharmacokinetic model.[4]

In conclusion, the time course of plasma fentanyl concentration was well-described by a three-compartment mammillary model using an allometric expression. The median MEC and MEAC in patients who underwent major intra-abdominal open surgeries were 0.7 and 1.0 ng ml^{-1}, respectively. These results provide a scientific basis for the use of fentanyl for acute postoperative pain management in surgical patients. Based on the MEAC results, the potency ratio of oxycodone to fentanyl was 75:1.

Authors' contributions

Study design: JYB, MYK, BMC, GJN
Data collection: JYB, YHL, BMC
Data analysis and interpretation: JYB, MYK, EKL, BMC
Contributed to the writing of the manuscript, provided critical revisions, and approved the final version: all authors.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2020.06.066.

Declarations of interest

The authors declare that they have no conflicts of interest.

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