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Population Pharmacokinetics of Fentanyl in the Critically Ill

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Abstract

Objective—To characterize fentanyl population pharmacokinetics in patients with critical illness and identify patient characteristics associated with altered fentanyl concentrations.

Design—Prospective cohort study.

Setting—Medical and surgical ICUs in a large tertiary care hospital in the United States.

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Patients—Patients with acute respiratory failure and/or shock who received fentanyl during the first five days of their ICU stay.

Measurements and Main Results—We collected clinical and hourly drug administration data and measured fentanyl concentrations in plasma collected once daily for up to five days after enrollment. Among 337 patients, the mean duration of infusion was 58 hours at a median rate of 100 µg/hr. Using a nonlinear mixed-effects model implemented by NONMEM, we found fentanyl pharmacokinetics were best described by a two-compartment model in which weight, severe liver disease, and congestive heart failure most affected fentanyl concentrations. For a patient population with a mean weight of 92 kg and no history of severe liver disease or congestive heart failure, the final model, which performed well in repeated 10-fold cross-validation, estimated total clearance (CL), intercompartmental clearance (Q), and volumes of distribution for the central (V_1) and peripheral compartments (V_2) to be 35 (95% confidence interval: 32 to 39) L/hr, 55 (42 to 68) L/hr, 203 (140 to 266) L, and 523 (428 to 618) L, respectively. Severity of illness was marginally associated with fentanyl pharmacokinetics but did not improve the model fit after liver and heart disease were included.

Conclusions—In this study, fentanyl pharmacokinetics during critical illness were strongly influenced by severe liver disease, congestive heart failure, and weight, factors that should be considered when dosing fentanyl in the ICU. Future studies are needed to determine if data-driven fentanyl dosing algorithms can improve outcomes for ICU patients.

Keywords

sedation; mechanical ventilation; fentanyl; pharmacokinetics; intensive care

Fentanyl is a synthetic opioid analgesic commonly prescribed in the intensive care unit (ICU) for its ability to provide both analgesia and sedation to critically ill patients (1). Recent Society of Critical Care Medicine clinical practice guidelines for the management of pain, agitation, and delirium in the ICU—which recommend “provision of adequate analgesia” prior to use of sedatives—include fentanyl among several opioids suggested as first-line analgesics (2). In addition to analgesia, fentanyl can have a significant sedative effect, which may be helpful when precisely titrated but harmful if the drug contributes to oversedation. A large body of evidence has shown that oversedation may lead to worse clinical outcomes, including increased mortality (3, 4). Therefore, the pharmacokinetics of fentanyl must be carefully considered when prescribing this potent medication to vulnerable ICU patients.

A number of factors likely contribute to variability in fentanyl metabolism during critical illness. Hepatic drug-metabolizing enzymes, including cytochrome (CYP) P450 enzymes (with CYP3A4 primarily responsible for metabolizing fentanyl in humans) (5), are reduced in quantity and function in older patients (6), who make up the majority of ICU patients. Moreover, critical illness often results in failure of organs that affect pharmacokinetics, e.g., the liver, kidney, and heart. Yet, though population pharmacokinetic studies of fentanyl have been conducted in several populations, including healthy volunteers (7), burn patients (8), coronary artery bypass graft patients (9), and liver transplant patients (10), the

pharmacokinetics of fentanyl for the heterogeneous medical/surgical ICU patient population has not been well studied.

We therefore investigated the population pharmacokinetics of fentanyl in a large cohort of critically ill patients who received fentanyl via infusions or multiple bolus doses. Our objective was to characterize fentanyl population pharmacokinetics in an ICU cohort and identify patient characteristics associated with altered fentanyl concentrations.

MATERIALS AND METHODS

Study Design and Population

We conducted this prospective cohort study concurrently with the Bringing to Light the Risk Factors and Incidence of Neuropsychological Dysfunction in ICU Survivors (BRAIN-ICU) Study (11), which investigated risk factors for long-term cognitive impairment after critical illness. In the current study, we included all BRAIN-ICU subjects who received fentanyl at Vanderbilt University Medical Center during the first five days of their ICU stay. Adults admitted to the medical or surgical ICU with respiratory failure, cardiogenic shock, or septic shock were eligible for the BRAIN-ICU Study unless they met one of the following exclusion criteria: recent significant critical illness (any mechanical ventilation in an ICU during the 2 months preceding the current admission, >5 days in an ICU during the 30 days preceding the current admission, or >72 hours with organ dysfunction during the current admission); severe dementia or suspected anoxic brain injury; moribund status (with death expected within 24 hours); or expected inability to attend or participate in follow up assessments due to blindness, deafness, inability to speak English, incarceration, homelessness, active substance abuse, psychotic mental illness, suicidal ideation, or residence greater than 200 miles from Nashville. Detailed descriptions of inclusion/exclusion criteria are available in a previous publication (11).

The institutional review board at Vanderbilt University approved the study protocol. We obtained informed consent from all participants or an authorized surrogate (if the participant lacked capacity to consent) at the time of study enrollment. Additionally, we obtained informed consent from participants initially enrolled by a surrogate once the participant regained decision-making capacity.

Study Procedures

In this observational study, fentanyl and all other medications were administered solely at the discretion of the treating ICU team. We collected demographic and clinical data from the electronic medical record and extracted detailed hourly drug administration data from the electronic medication administration record for use in the pharmacokinetic analysis. We collected blood in EDTA tubes once daily for up to five days after enrollment whenever the participant had received fentanyl via continuous infusion during the 48 hours preceding the date of blood collection and/or via two or more intermittent boluses during the 24 hours preceding the date of blood collection. Within one hour of collection, we centrifuged the tubes and removed the plasma, storing it at –80 degrees Celsius until batched measurement of fentanyl plasma concentrations were performed. Plasma concentrations of fentanyl were

measured at Aegis Sciences Corporation (Nashville, TN) using validated liquid chromatography-tandem mass spectrometry (LC-MS-MS) procedures (12, 13), as described in detail in Supplemental Digital Content 1.

Population Pharmacokinetic Analysis

We analyzed population pharmacokinetics of fentanyl using a nonlinear mixed-effects model implemented by NONMEM® version VII (14). All fentanyl doses were included in the analysis, with boluses distinguished from infusions by specifying different rates of administration (i.e., instantaneous vs. zero-order infusion rate). Our approach to selecting the base model without covariates is described in detail in Supplemental Digital Content 1.

Covariate Analysis

From the selected base model, we explored the covariates described herein using empirical Bayes estimates for pharmacokinetic parameters with both graphical and statistical methods. We then examined selected covariates for inclusion in the final covariate model, which we chose based on the objective function values in NONMEM (see Supplemental Digital Content 1 for details). We considered with the following candidate covariates, which we chose *a priori* based on previous research and biological plausibility. Covariates collected once using hospital admission records included age, gender, weight, overall burden of chronic disease per the Charlson Comorbidity Index (15), chronic kidney disease, moderate/severe liver disease, and congestive heart failure, the latter three identified when treating physicians' notes indicated the comorbidity of interest was present prior to or during the current illness. We differentiated moderate/severe (henceforth referred to as severe) liver disease from mild liver disease using previously published definitions (16). Specifically, we considered severe liver disease present if a patient currently or previously had hepatic coma, portal hypertension, esophageal varices, or other sequelae of chronic liver disease. Since no patient had a history of both severe liver disease and congestive heart failure and their associations with pharmacokinetic parameters were similar, we also examined a composite variable for history of either. Covariates collected once based on ICU admission records included ICU type (medical vs. surgical) and severity of illness per the Acute Physiology and Chronic Health Evaluation (APACHE) II (17). Finally, covariates collected daily throughout the ICU stay included severe sepsis, bilirubin, creatinine, and daily severity of illness per the Sequential Organ Failure Assessment (SOFA) (18).

In addition to the aforementioned covariates, we also assessed in *post hoc* analyses whether CYP3A inhibitors or inducers were associated with fentanyl clearance. Using electronic medication administration records, we identified patients in our cohort who received fentanyl concomitantly with a medication known to be a strong inhibitor or inducer of CYP3A (19). We then used linear regression to determine whether the CYP3A inhibitors or inducers that were used concomitantly with fentanyl in >10% of patients were associated with individual-specific fentanyl clearance.

Model Validation

We used 10-fold cross-validation to internally validate the model's prediction of fentanyl plasma concentrations (20, 21), as described in detail in Supplemental Digital Content 1. We

then plotted observed fentanyl concentrations and the median predicted fentanyl concentration (and the 95% prediction interval) using the 2.5th, 50th, and 97.5th concentrations predicted in cross-validation models.

Sensitivity Analysis

Since we included all fentanyl doses, including both bolus and infusion doses, in our population pharmacokinetic analysis, we performed a sensitivity analysis to assess whether including bolus doses altered the model. Since only 7% of the cohort received only bolus doses, an analysis using only their data would be greatly limited in statistical power, so we performed a sensitivity analysis using data from the 65% of patients who received fentanyl via infusion only to determine whether results were similar to those of the model using all fentanyl doses.

Simulations

Using the estimated parameters from the final model, we performed simulations to examine predicted fentanyl plasma concentrations for specific patient populations. We assumed that fentanyl was continuously infused for 3 days with a zero-order rate of 100 µg/hr, which was the median infusion rate for the study cohort. We also assumed four 100 µg bolus doses were given. To make the effect of these boluses more visible in the predicted concentration profile, we chose the dose of 100 µg, which was the 75th percentile dose of boluses in our cohort, and we chose to give four boluses, which was the 75th percentile of the number of boluses received in our cohort. The predicted concentration profiles were obtained for patient populations with and without history of severe liver disease or congestive heart failure who were in the 10th, 50th and 90th percentiles of weight in our patient population. The simulations were performed using the programming language R version 3.1.0 (22) and NONMEM® version VII (14).

RESULTS

Patient Characteristics and Fentanyl Exposure

Between March 2007 and May 2010, we enrolled 521 patients in the BRAIN-ICU Study at Vanderbilt University; 337 of these received fentanyl and are included in the current study (Table 1). A high percentage of the study population, which was primarily Caucasian and had a mean age of 57 years, was overweight or obese. One in four patients had a history of severe liver disease or congestive heart failure. Both APACHE II at enrollment and SOFA throughout the ICU stay indicated a high severity of illness (Table 1).

The number of fentanyl plasma concentration measurements per patient (which were limited by protocol to 5) ranged from 1 to 5; 65% of patients had fentanyl plasma concentration measured on at least 3 days, whereas 10% had only one measurement. During the 5-day study period, the mean duration of fentanyl infusion was 58 hours, and the mean and median infusion rates were 131 and 100 µg/hr, respectively. The median number of boluses per patient in the study period was 2 boluses, and the 75th percentile was 4 boluses; the median and the 75th percentile doses for boluses per patient were both 100 µg.

Pharmacokinetic Model and Factors affecting Fentanyl Pharmacokinetics

A two-compartment model described the fentanyl pharmacokinetics substantially better than a one-compartment model; thus, a two-compartment model was chosen as the base model. The estimates of pharmacokinetic parameters for the base and final models as well as the patient characteristics that affected fentanyl pharmacokinetics are summarized in Table 2.

Patients' weight and history of severe liver disease or congestive heart failure were included in the final covariate model, which greatly improved model fit compared with the base model; the objective function value decreased by 68 (from 667 to 599). Weight was a very strong predictor in explaining interindividual variability for both clearance (CL) and volume of distribution for the peripheral compartment (V_2). Whereas severe liver disease and congestive heart failure each individually improved the model with similar magnitude in explaining interindividual variability in CL, a composite variable for history of either severe liver disease or congestive heart failure was a much stronger predictor in terms of power since the composite variable includes a larger group of patients (25.8%) than either variable considered separately (10.4 and 15.4% for severe liver disease or congestive heart failure, respectively), and no patient had both conditions. As such, the composite variable was included in the final model. The final covariate model is presented as follows:

$$CL_i = [\theta_1 + \theta_2(Wgt_i - 92) + \theta_3SLDCHF_i] \times \exp(\eta_i^{CL})$$

$$V_{1i} = \theta_6 \times \exp(\eta_i^{V1})$$

$$V_{2i} = [\theta_4 + \theta_5(Wgt_i - 92)] \times \exp(\eta_i^{V2})$$

$$Q = \theta_7$$

where Wgt_i is weight; $SLDCHF_i$ is the composite score of history of severe liver disease or congestive heart failure; CL_i , V_{1i} and V_{2i} are the individual-specific parameters corresponding to clearance (CL), volume of distribution for the central compartment (V_1) and volume of distribution for the peripheral compartment (V_2); Q is intercompartmental clearance; and η_i^{CL} , η_i^{V1} and η_i^{V2} are random variables explaining interindividual variability for CL, V_1 and V_2 , which follow a normal distribution with mean zero and variance of ω^2_{CL} , ω^2_{V1} and ω^2_{V2} .

Body weight was within one standard deviation of the mean (i.e., 92 ± 33 kg) in 265 (79%) patients who contributed 828 fentanyl concentration measurements; 193 (contributing 614 fentanyl concentration measurements) of these had neither severe liver disease nor congestive heart failure, whereas 30 (with 93 measurements) had severe liver disease and 42 (with 121 measurements) had congestive heart failure. The estimates of CL, Q , V_1 , and V_2 for a patient population with a mean weight of 92 kg and no history of severe liver disease

and congestive heart failure were 35 L/hr (95% confidence interval [CI]: 32 to 39 L/hr), 55 L/hr (95% CI: 42 to 68 L/hr), 203 L (95% CI: 140 to 266 L), and 523 L (95% CI: 428 to 618 L), respectively. These pharmacokinetic parameters varied substantially between individual patients, with the interindividual variability (in %CV) for CL, V_1 , and V_2 being 64%, 84%, and 69%, respectively. These percentages were smaller than those from the base model since covariates explained part of the variability in the parameters.

After inclusion of weight and history of severe liver disease or congestive heart failure, no other covariate improved model fit. SOFA score, for example, was marginally associated with individual-specific CL but did not greatly improve the model fit once a history of severe liver disease and congestive heart failure was included in the model. SOFA score was therefore not included in the final model. Similarly, neither chronic kidney disease nor APACHE II were associated with individual-specific CL and neither improved model fit. Most CYP3A inhibitors and inducers were rarely administered to patients receiving fentanyl in our cohort (Table 1). Fluconazole and diltiazem were co-administered with fentanyl in more than 10% of patients, but neither was significantly associated with individual-specific fentanyl CL ($p=0.08$ and 0.22 , respectively).

The goodness-of-fit plots for model checking are presented in Figure 1. The large variability in population predicted values (Figure 1A) is significantly reduced in the individual predicted values (Figure 1B). Although some values appear to be over-predicted, the plots of observed vs. predicted values are primarily evenly distributed along the line of equality in Figures 1A and 1B, indicating good model fit. The conditional weighted residuals shown in Figures 1C and 1D serve as a model diagnostic tool. When the residuals are plotted over time (Figure 1C), they should be symmetrically distributed around the line of zero over time without an obvious trend. Additionally, the distribution of the residuals (Figure 1D) should be approximately symmetrical with center at zero, although slightly skewed, and most lie within ± 3 . Figures 1C and 1D show no evidence of obvious model misspecification. Thus, the goodness-of-fit plots and the conditional weighted residuals shown in Figure 1 indicate that the final model was fit to the data reasonably well.

Model Validation and Sensitivity Analysis

Figure 2 shows the results of repeated 10-fold cross-validation. Nearly all observed fentanyl plasma concentrations fell within the 95% prediction region, suggesting that the final model predicted fentanyl plasma concentrations reasonably well. Additionally, estimates of pharmacokinetic parameters obtained in sensitivity analysis using data from the 65% of patients who received only infusion doses were very similar to those obtained using data from all 337 patients (Supplemental Digital Content 2). Thus, the inclusion of multiple bolus doses, at least with the frequency and doses given to patients in our cohort, did not affect the estimates of model parameters.

Predicted Concentration Profiles

Figure 3 shows the predicted concentration profiles for patient populations without (A) and with (B) history of severe liver disease or congestive heart failure who are in the 10th, 50th and 90th percentiles of weight of the study population (59, 86 and 128 kg, respectively).

Figure 4 also shows the predicted concentration profiles, but the profiles are presented as percent of the profile for patients with the median weight and no history of severe liver disease or congestive heart failure. The lower a patient's weight, the lower their fentanyl clearance, resulting in the higher plasma concentrations than expected. If a patient had any of history of severe liver disease or congestive heart failure, predicted plasma concentrations would be much higher than among those who had no history of these comorbidities.

DISCUSSION

In this large, prospective cohort study, we examined population pharmacokinetics of fentanyl in medical/surgical ICU patients and identified three patient characteristics that affect fentanyl pharmacokinetics during critical illness: weight, a history of severe liver disease, and a history of congestive heart failure. Though sedatives such as midazolam, propofol, and dexmedetomidine have undergone population pharmacokinetic study (23–27), there has not been a similar investigation of fentanyl, despite its frequent use for analgesedation in the ICU. To our knowledge, this study is the first to examine fentanyl population pharmacokinetics in critically ill adult ICU patients.

We found that weight was the most important factor that affected both CL and V_2 . In fact, our model estimates that after just one day of a continuous infusion, plasma concentrations of fentanyl will be approximately 50% higher in patients at the 10th percentile of weight than in those at the 90th percentile. It has been well known that weight affects the pharmacokinetic profile of many drugs including analgesics. Lipophilic agents such as fentanyl are significantly affected by increased fat-to-lean mass ratios because of increased volume of distribution (28). Though these data may be taken to suggest weight-based dosing of fentanyl may be appropriate in the ICU, an investigation of surgical patients found that weight-based dosing overestimated fentanyl dosing requirements in obese patients (29). Clinicians should be aware that obese patients may need higher overall doses of fentanyl, but strict weight-based dosing may result in excessive fentanyl administration and should therefore be avoided. Alternatively, lean patients are likely to require less fentanyl than is typically used in the ICU, so clinicians should be especially cautious about overdosing such patients.

We additionally found that a history of severe liver disease or congestive heart failure reduced fentanyl clearance substantially. Our results regarding liver disease are not surprising since fentanyl has been shown to have a high hepatic extraction ratio (0.7–1.0 in healthy volunteers) and is metabolized almost exclusively in the liver (30). At least one previous study, however, showed clearance was not significantly affected by cirrhosis among surgical patients who received a single bolus of fentanyl (31). Unlike such surgical patients, however, those in our cohort (as in most ICUs) received either a longer period of continuous infusion or multiple boluses of fentanyl. Like many lipophilic drugs, fentanyl redistributes to the peripheral tissues and accumulates when infused over a longer period of time, leading to a longer half-time than is the case with shorter infusions. Our results suggest clinicians should be especially cautious when using a fentanyl infusion or multiple boluses in the setting of liver dysfunction or congestive heart failure, supporting recommendations outlined in a recent review (32), which highlighted the need for data regarding the

pharmacokinetics of continuously infused fentanyl in cirrhotic patients. Similar to severe liver disease, congestive heart failure was also a risk factor for reduced fentanyl clearance in our study, a novel finding suggesting judicious dosing is warranted in the setting of heart failure. Though not examined in our study, the mechanism underlying this finding may be decreased hepatic blood flow secondary to a lower cardiac output. Hepatic metabolism of fentanyl may also be altered during use of medications that inhibit or induce CYP3A. We found no significant associations between CYP3A inhibitor/inducer use, but these medications were rarely co-administered with fentanyl in our cohort and should therefore be examined in future studies as should CYP3A genetic variation.

Though estimates of pharmacokinetic parameters from different models (e.g., 2- vs. 3-compartmental models) and studies with different designs (e.g., sparse vs. dense sampling) may not be directly comparable to ours, our estimate of total clearance was similar to those from several studies (8, 33–35). We did not, however, find strong associations between pharmacokinetic parameters and previously reported factors that might affect fentanyl pharmacokinetics such as age, bilirubin, and a history of chronic kidney disease. A previous comparison between young and elderly adult patients, for example, found fentanyl concentrations were higher in the elderly due to altered fentanyl clearance (36). In contrast, we found no association between age and pharmacokinetic parameters possibly because our study population had fewer younger patients than previously studied surgical cohorts. Additionally, the effects of chronic and acute organ dysfunction may have a larger effect on drug pharmacokinetics and thus reduce the relative effect of age. Despite the high frequency of renal failure during critical illness, our model is in agreement with previous studies reporting fentanyl concentrations were not reduced in patients with renal failure (37, 38).

Our study has some notable strengths and limitations. The major limitation is that the drug level sampling was sparse, only once a day for up to 5 days. Thus, pharmacokinetic parameters may not be precisely estimated. In addition, the increased variability due to sparse sampling may have led to missing some patient characteristics that may in fact affect fentanyl pharmacokinetics during critical illness. Also, data on some characteristics that may affect fentanyl clearance, e.g., chronic opiate dependence, hypoalbuminemia, etc., were not available. The finding that weight, severe liver disease, and congestive heart failure were significantly associated with fentanyl pharmacokinetics despite sparse sampling indicates the importance of these characteristics. We did not use specific definitions for these comorbidities, instead relying on treating physicians to identify relevant chronic medical conditions, but any misclassification of these variables was likely to attenuate the effect of these characteristics in our pharmacokinetic model. Another limitation was that the study was performed in the ICU, an uncontrolled environment where numerous measured and unmeasured factors can influence pharmacokinetic parameters as well as data collection. The number of samples contributed per patient, for example, may be influenced by severity of illness since those who improve more rapidly are likely to receive fentanyl for a shorter duration. The ICU setting, however, is also one of our investigation's major strengths; given the real-world, clinical context within which our data were derived, the results are much more generalizable to critically ill patients than those from studies conducted in carefully controlled environments.

Ideally, the management of pain, agitation, and delirium in the ICU should use a personalized approach that delivers precisely the right medications to each patient in the right dose at the right time (39). In current practice, however, analgesics and sedatives are often delivered at similar doses to patients with widely varying characteristics. The use of validated sedation scales and protocols that seek to minimize sedation have resulted in significant progress in this area of critical care, but oversedation and (less frequent but still important) undertreatment of pain and agitation remain a common challenge in the ICU. Though our results suggest that weight and history of liver and heart disease should be considered when dosing fentanyl in the ICU, our investigation was not designed to examine the efficacy of such an approach nor did it examine which clinical outcomes (e.g., pain control, level of arousal, etc.) are affected by fentanyl plasma concentration. Future studies are needed to identify outcomes most likely to be improved by tighter control of fentanyl concentrations and to determine whether pharmacokinetic data-driven dosing algorithms can improving outcomes for this vulnerable patient population.

CONCLUSIONS

In conclusion, we found in this large prospective cohort study that fentanyl pharmacokinetics during critical illness are strongly influenced by a history of severe liver disease, a history of congestive heart failure, and weight, factors that should be considered when dosing fentanyl in the ICU. Further studies are needed to validate our results and determine if data-driven dosing algorithms can improve the clinical outcomes of ICU patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Observed plasma fentanyl concentrations versus population predicted plasma fentanyl concentrations (A) and individual predicted plasma fentanyl concentrations on log-log axes (B); Conditional weighted residuals versus time after dose (C); Histogram of conditional weighted residuals (D).

Figure 2.

Observed and predicted fentanyl concentrations as determined by repeated 10-fold cross-validation. All observed fentanyl plasma concentrations that were measured during the 5-day study period are shown as black empty dots. Additionally, the orange line (and gray band) shows the median (and 95% prediction interval) fentanyl plasma concentration predicted in cross-validation models; i.e., the orange line shows the 50th percentile of predicted concentrations at a given point in time, and the lower and upper bounds of the gray band show the 2.5th and 97.5th concentrations predicted at a given point in time.

Figure 3.

Predicted fentanyl concentrations over time for patients weighing 59, 86, or 128 kg, which were the 10th, 50th, and 90th percentiles in our study population: (A) no history of severe liver disease (SLD) or congestive heart failure (CHF); (B) any history of severe liver disease (SLD) or congestive heart failure (CHF). In these simulations, fentanyl is continuously infused at 100 µg/hr for 3 days, after which the infusion is stopped (gray arrow), and four 100 µg bolus doses (some of which are indicated by orange arrows) are given at random times.

Figure 4.

Predicted fentanyl concentrations over time for patients weighing 59, 86, or 128 kg, which were the 10th, 50th, and 90th percentiles in our study population, presented as percent of the predicted fentanyl concentrations for patients with the median weight: (A) no history of severe liver disease (SLD) or congestive heart failure (CHF); (B) any history of severe liver disease (SLD) or congestive heart failure (CHF). In these simulations, fentanyl is continuously infused at 100 µg/hr for 3 days, after which the infusion is stopped, and four 100 µg bolus doses are given at random times.

Table 1Demographics and Clinical Characteristics^a

Characteristics	Cohort (N=337)
Age (yr)	57 ± 15 (19 to 87)
Female	156 (46%)
Weight (kg)	92 ± 33 (37 to 273)
Charlson Comorbidity Index	2.6 ± 2.3 (0 to 11)
Comorbid illnesses	
Severe liver disease	35 (10%)
Congestive heart failure	52 (15%)
Severe liver disease or congestive heart failure	87 (26%)
Chronic kidney disease	49 (15%)
ICU type	
Surgical	170 (50%)
Medical	167 (50%)
APACHE II at enrollment	27 ± 8 (2 to 56)
Sepsis in the hospital ^b	238 (70.6%)
SOFA, median in the ICU ^c	10 ± 3 (3 to 21)
Bilirubin, median mg/dL in the hospital ^c	1.5 ± 2.5 (0 to 22)
Creatinine, median mg/dL in the hospital ^c	1.9 ± 1.7 (0.3 to 12.9)
Fentanyl exposure	
Bolus only	22 (7%)
Bolus and infusion	96 (28%)
Infusion only	219 (65%)
Total duration (hr)	58 ± 38 (1 to 144)
Infusion rate (µg/hr) ^d	131 ± 93 (13 to 750)
Fentanyl plasma concentration measurements	
1	35 (10%)
2	84 (25%)
3	79 (23%)
4	63 (19%)
5	76 (23%)
Concomitant CYP3A inhibitor or inducer use	
Fluconazole	42 (13%)
Diltiazem	37 (11%)
Ciprofloxacin	12 (4%)
Voriconazole	9 (3%)
Erythromycin	8 (2%)
Rifampin	6 (2%)
Other ^e	4 (1%)

^a Categorical variables are reported at n (%), and all other variables are reported as mean $\pm$ standard deviation (range).

^b Sepsis was identified using international consensus criteria on a daily basis during the patient's hospitalization for up to 30 days.

^c Because these variables are measured repeatedly within the same patient and are therefore not independent within a patient, summary statistics that are calculated based on individual measurements do not appropriately reflect population parameters. The median value was therefore calculated for each patient, and then summary statistics for the medians were calculated across all patients.

^d The summary statistics were calculated based on individual.

^e Two patients received phenytoin, one received itraconazole, and one received ritonavir.

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Table 2

Estimates of Parameters for the Base and Final Pharmacokinetic Models

Covariate Model (Obj = 599)		Base Model (Obj = 667)			
Parameter	Estimates (SE)	95% CI ^a	Parameter	Estimates (SE)	95% CI
CL = $\theta_1 + \theta_2 W_{gt_c} + \theta_3 SLDCHF$					
θ_1	35 (2)	32 to 39	CL	32 (1)	29 to 34
θ_2	0.19 (0.05)	0.10 to 0.28			
θ_3	-10.6 (2.4)	-15.2 to -6.0			
V_1	203 (32)	140 to 266	V_1	252 (34)	186 to 318
$V_2 = \theta_4 + \theta_5 W_{gt_c}$			V_2	474 (46)	385 to 563
θ_4	523 (49)	428 to 618			
θ_5	7.1 (1.7)	3.9 to 10.4			
Q	55 (7)	42 to 68	Q	43 (5)	32 to 53
ω^2_{CL} (%CV)	64 (19)	59 to 70	ω^2_{CL} (%CV)	69 (22)	62 to 76
ω^2_{V1} (%CV)	84 (52)	43 to 111	ω^2_{V1} (%CV)	88 (46)	59 to 109
ω^2_{V2} (%CV)	69 (28)	57 to 80	σ^2_{V2} (%CV)	78 (37)	59 to 94
$\sigma^2_{proportional}$ (%CV)	33 (7)	32 to 35	$\sigma^2_{proportional}$ (%CV)	33 (7)	32 to 35
$\sigma^2_{additive}$ (ng/mL)	0.02 (0.03)	0.0 to 0.04	$\sigma^2_{additive}$ (ng/mL)	0.04 (0.03)	0.0 to 0.06

Abbreviations: Obj, the objective function value; CL, total clearance (L/hr); Q, intercompartmental clearance (L/hr); V_1 , volume of distribution for the central compartment (L); V_2 , volume of distribution for the peripheral compartment (L); W_{gt_c} , weight centered at the mean of 92, (weight - 92); SLDCHF, any history of severe liver disease (SLD) or congestive heart failure (CHF); ω^2_{CL} , ω^2_{V1} and ω^2_{V2} , the estimates of variance for η_{CL} , η_{V1} and η_{V2} , respectively; $\sigma^2_{proportional}$ and $\sigma^2_{additive}$, the estimates of variance for proportional and additive residual errors, respectively.

^aThe 95% confidence intervals (CIs) were obtained by a normal approximation.