Pharmacokinetic Model-driven Infusion of Fentanyl in Children

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Background: This study determined the accuracy of previously defined adult fentanyl pharmacokinetics in children having surgery; from this population, the pharmacokinetics of fentanyl were characterized in children when administered via a computerized assisted continuous-infusion device.

Methods: Twenty children between the ages of 2.7 and 11.7 scheduled to undergo elective noncardiac surgery were studied. After induction, anesthesia was maintained with 60% nitrous oxide in oxygen supplemented with fentanyl (n = 10) or fentanyl plus isoflurane (n = 10). Fentanyl was administered via computerized assisted continuous-infusion to target concentrations determined by clinical requirements. Plasma fentanyl concentrations were measured and used to evaluate the performance of the fentanyl pharmacokinetics and then to determine a new set of pharmacokinetic parameters and the variance in the context-sensitive half-times simulated for these patients.

Results: The original adult fentanyl pharmacokinetics resulted in a positive bias (10.4%), indicating that measured concentrations were mostly greater than predicted. A two-compartment model with age and weight as covariates provided the optimal pharmacokinetic parameters. These resulted in a residual performance error of -1.1% and a median absolute performance error of 17.4%. The context-sensitive times determined from this pediatric population were considerably shorter than the context-sensitive times previously published for adults.

Conclusions: The pharmacokinetics of fentanyl administered by computerized assisted continuous-infusion differ between adults and children. The newly derived parameters are probably more suitable to determine infusion schemes of up to 4 h in children between the ages of 2 and 11 y. (Key words: Anesthetics, intravenous: fentanyl. Pharmacokinetics. Pediatrics. Computers.)

FENTANYL is commonly administered during anesthesia in both adults and children. The disposition of fentanyl in adults has been described many times, and more recently these pharmacokinetic parameters have been tested prospectively using pharmacokinetic model-driven intravenous drug-delivery devices.1-2 The disposition of fentanyl in pediatric patients has not, however, been well described. Several studies in neonates and children report age-dependent differences in the pharmacokinetic parameters of fentanyl.1-3 Because fentanyl is commonly administered to pediatric patients, we wished to describe its disposition in children so that more appropriate dosing could be achieved.

Classically, a drug’s disposition is determined by characterizing its concentration-time profile after either a bolus dose of the drug or a rapid infusion. The accuracy with which each of these parameters is determined depends on the sampling frequency and the duration of the sampling period.1 Thus the utility of the pharmacokinetic parameters calculated by either of these methods may be less accurate in determining infusion schemes for administering drug to attain target plasma concentrations for periods longer than observed in the initial study. An infusion technique targeting concentrations within the concentration range and the duration that is likely to be used clinically will provide the most accurate determination of the pharmacokinetic parameters for a targeted infusion.1,2 Computerized assisted continuous-infusion (CACI) devices use a set of pharmacokinetic parameters to deliver an intravenous drug to a target concentration.3 These devices also record infusion rates so that it is possible from plasma sample data to determine the behavior of a drug in the population to whom the drug was administered.

Methods

Approval was obtained from the University of Virginia Institutional Review Board. Written informed consent was obtained for 20 children. The children were scheduled for procedures requiring anesthetic care. Parents of children with chronic or acute medical problems were excluded.

Anesthesia was induced with thiopental and maintained with isoflurane in oxygen, nitrous oxide, and fentanyl. Fentanyl was delivered equally as an intravenous bolus dose or as a constant rate infusion. Anesthesia was maintained sedation was maintained with thiopental and/or midazolam. Fentanyl was delivered equally as a computer-assisted continuous infusion (CACI) device or as a constant rate infusion.

Tracheal intubation was performed by a certified pediatric anesthesiologist. Motor and respiratory function was monitored by a trained registered nurse. Arterial and central venous lines were placed. The principles of cardiorespiratory stability were maintained. The children were then randomized to receive fentanyl 60 ng/kg/min/week or 100 ng/kg/min. Both groups received the same fentanyl bolus and the same anesthetic maintenance.

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whom the drug was given. We used the CACI device with adult fentanyl pharmacokinetic parameters as described by McClain and Hug in a pediatric population.

The purpose of the study was to determine the accuracy of an adult pharmacokinetic set with CACI in children having surgery and, from these data, to determine the pharmacokinetic parameters of fentanyl that most accurately described its disposition in this population of children.

Methods

Approval for this study was obtained from the Duke University Institutional Review Board for human studies. Written informed parental consent was obtained for 20 children between the ages of 2 and 11 y who were scheduled for elective noncardiac surgery that required an arterial line for hemodynamic monitoring. Children were excluded for consideration if there was clinical and laboratory evidence of hepatic or renal disease.

Anesthesia was induced with either intravenous sodium thiopental or via mask using nitrous oxide, oxygen, and incremental increases in inspired halothane concentration. After loss of consciousness, anesthesia was maintained with 60% nitrous oxide in oxygen. An intraarterial catheter was placed for hemodynamic monitoring and to obtain arterial blood samples for subsequent measurement of plasma fentanyl concentrations.

Tracheal intubation was facilitated with a nondepolarizing neuromuscular blocker, and ventilation was controlled to maintain an end-tidal carbon dioxide pressure of 30 to 35 mmHg. The children's temperatures were maintained at more than 36°C. The children were assigned to two sequential groups of 10 each. The first ten children (group A) had anesthesia maintained with 60% nitrous oxide and oxygen with fentanyl administered via CACI. The second ten children (group B) received fentanyl plus 0.5% isoflurane.

Based on previous studies in adults, a target plasma concentration of fentanyl of 3 to 7 ng/ml was deemed appropriate for skin incision. During surgery, the target plasma concentration of fentanyl was varied to maintain an adequate depth of anesthesia. The target concentration of fentanyl was increased by 1 to 2 ng/ml if there were signs of inadequate anesthesia as indicated by either a 15% increase above baseline blood pressure or heart rate or other autonomic signs of inadequate anesthesia. If after a 15-min period there were no such signs, the target plasma fentanyl concentration was decreased by 0.5 to 1 ng/ml. Whenever possible, blood samples were obtained at 0, 1, 3, 5, and 10 min after each adjustment in the fentanyl target concentration or at pseudo-steady state to determine fentanyl arterial plasma concentrations. The number of blood samples obtained were limited by the child's age, starting hematocrit concentration, and anticipated blood loss. Because of these limitations, most of the blood samples were taken at pseudo-steady state conditions. A maximum of ten 2-ml arterial samples was obtained from each patient. The blood samples were immediately placed on ice, centrifuged within 3 h, and the plasma was stored at -70°C until radioimmunoassay.

Initial evaluation involved a retrospective analysis of the performance of the original pharmacokinetic parameters used in the CACI pump program. The accuracy of the pharmacokinetics used with CACI were assessed by calculating the percentage performance error (%PE), and absolute performance error (%APE) for each sample. The median % PE and median % APE were calculated for each patient and for the entire study population.

New sets of pharmacokinetic parameters were derived using PKPD Tools with XLMEM, ANALYZE, and NONMEM* (Version IV). NONMEM analysis was performed using a prediction subroutine (NMVCLDRG)** configured with a log-normal variance model on the interindividual error term of the kinetic parameters (V1, V2, CI1[V1·K10], and CI2[V1·K12]) and "constant c.v." variance model for the intridual error term. NONMEM analysis did not include first-order conditional expectation and interaction between etas and epsilon, because they did not improve the indicators of model performance described below.

Initially, naive pooled data kinetics were derived for both two- and three-compartment models. These estimates were then used to derive a mixed-effects model with no covariates for both two- and three-compartment models. The two-compartment model was selected based on the value of the objective function,

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[2] Written by Steven Shafer and available by anonymous FTP/URL at the locations noted previously.


[4] Written by Steven Shafer and available by anonymous FTP/URL at the locations noted in previous footnotes.

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plots of residual errors, standard errors of the estimates, and examination of the unit disposition functions based on the empirical individual (Bayesian) estimates plotted together with the unit disposition functions based on the typical population values.

After selecting the two-compartment model, we investigated various covariate models, starting with a model in which all parameters were weight proportional. A generalized additive model search \cite{ginsberg2008} was then performed using SPlus for Windows \cite{fiser2012} (version 3.2). Covariate models using age, weight, height, lean body mass, body surface area, sex, and technique (isoflurane vs. nitrous oxide/narcotic) were examined using a bidirectional search. Thirty-five different models were tried by the program. Models were selected based on minimization of the Akaike Information Criterion. No significant nonlinear correlations were found. The initial covariate model included a linear function of age and weight on each of the four parameters and was structured with the age and weight of each child minus the population median values of each covariate plus an intercept term. The initial model was then run repeatedly, with each iteration performed by removing a single covariate term and examining the effect on the objective function and on the standard errors of the estimates. The final covariate model included weight on V1, age on V2, weight on CI1(V1·K10), and no covariates on CI2(V1·K12).

We also performed an internal cross-validation in the manner described by Fiset and associates.\cite{fiset2012} This involved rederiving the kinetic parameters for the covariate model with the data of one child removed from the total population. This was repeated for each of the children in turn, resulting in 20 different “N-1” pharmacokinetic parameter sets. The pharmacokinetic sets were used to predict prospectively the plasma concentrations for the child who was excluded from the population analysis. The performance of the “N-1” pharmacokinetic sets was evaluated in the same manner as the previously derived population pharmacokinetic sets.

The context-sensitive decrement time (CSDT), based on the method of Hughes and colleagues,\cite{hughes1994} for a 20%, 50%, and 80% decline in plasma concentrations using the covariate model for all the children and for typical population values were calculated. The CSDT predicts the time required for plasma concentrations of an intravenous drug to decline by a given percentage after a steady-state infusion of arbitrary length. The calculations were performed with a Microsoft Excel 5.0 VBA macro using the Solver function to estimate numerically the CSDT. In addition, the 20% and 50% CSDT, as computed for each child based on the individual (Bayesian) estimates for that child. The population means of the original individual estimates and the original adult pharmacokinetic parameters were calculated and compared.

The Student’s t test or the Mann Whitney U test were used (as appropriate) for comparison between the groups, and a probability value less than 0.05 was considered statistically significant.

### Results

The mean age of the children entered into the study was 6.4 y (range, 2.7 to 11 y). Their mean weight was 19.8 kg (range, 9.7 to 34.7 kg). The median duration of the fentanyl infusion was 3–5 min (range, 1 h and 14 min to 5 h and 45 min). Fourteen boys and six girls were enrolled in the study. Table 1 shows the demographic characteristics of the two groups. There were no statistical differences between the demographics of the two anesthetic groups.

<table>
<thead>
<tr>
<th>Table 1. Demographics</th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>5.7 ± 2.6</td>
<td>6.6 ± 2.2</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>19.8 ± 7.1</td>
<td>20.9 ± 7.0</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>117 ± 20</td>
<td>116 ± 20</td>
</tr>
<tr>
<td>Study duration (min)</td>
<td>232 ± 67</td>
<td>242 ± 80</td>
</tr>
<tr>
<td>Initial fentanyl measured (ng·mL⁻¹)</td>
<td>10.2 ± 3.8</td>
<td>6.0 ± 3.1</td>
</tr>
<tr>
<td>Initial fentanyl predicted (ng·mL⁻¹)</td>
<td>6.4 ± 2.9</td>
<td>4.2 ± 2.0</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

The mean initial fentanyl concentrations in group A and group B were 10.2 ± 3.8 and 6.0 ± 3.1 ng/mL, respectively, at the time of skin incision. There was no hypertension, tachycardia, or lacrimation at the time of skin incision in either group. The median of the individual median fentanyl concentrations required for clinical anesthesia was 6.6 ng/mL (range, 0.8 to 21.3 ng/mL) in group A. In group B, the concentrations were 4.3 ng/mL (range, 2.7 to 6.6 ng/mL).

Figure 1 shows that at each patient time point, one at the time of skin incision, and one at the end of the surgical procedure.

The mean concentration of fentanyl was consistently higher in group A compared to group B (median % difference, 21.9%; range, 3.3% to 54.2%). The bias is illustrated in Figure 2.

Table 2 summarizes the differences in the covariates. As for the covariates sex, age, weight, and body surface area, no differences were found between the two groups.

Similarly, there were no differences in the covariates sex, age, weight, and body surface area, no differences were found between the two groups.

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and for typical CSDT predictions of an individual percentage after 3 h. The calculations were conducted using Excel 5.0 (Microsoft). The 50% CSDTs and the individual predictions of the population parameters and the original parameter predictions were calculated for each patient. The $t$-test was used to test the difference between the calculated and observed values. A value of $p < 0.05$ was considered significant.

All patients were included in the study. The mean weight was $50.6 ± 10.3$ kg, and the median duration of the procedure was 96 min (range, 1 h 20 min to 3 h). All patients were given an opioid and a nonopioid analgesic. There were no significant differences in demographic variables between the two groups. There were no significant differences in the demographic variables between the two groups. There was no significant difference in the time of the procedure between the two groups. The time of the procedure was 96 min (range, 1 h 20 min to 3 h). There was no significant difference in the time of the procedure between the two groups. The time of the procedure was 96 min (range, 1 h 20 min to 3 h).

The measured plasma fentanyl concentrations were consistently greater than the CACI predicted plasma fentanyl concentrations. This resulted in a positive bias (median percentage error - MPE) of 10.4% and a 21.9% median percentage MPE (MAPE). The consistent positive bias is illustrated in the plot of the residual error (fig. 2).

Table 2 shows the derived pharmacokinetic parameters. As for the covariate model, the search for other covariates showed that anesthetic technique (isoflurane versus nitrous oxide - narcotic) was not a significant covariate.

Similarly, sex, height, lean body mass, and body surface area were not significant covariates or did not improve model performance any more than did age or weight. The simple weight-proportional model accounted for a 31% decrease of the percentage coefficient of variation (% CV) of both V1 and V2, compared with the model that did not include a covariate. Similarly, the covariate model accounted for a 9% decrease of the % CV of both V1 and C1H(V1 · K10), and 47% of the % CV of V2.

The initial pharmacokinetic parameters of the two-compartment model without covariates resulted in a median PE of +2% and an MAPE of 30%. The weight-proportional model resulted in an PE of +2% and MAPE of 23% and the covariate model resulted in an PE of −1.1% and an MAPE of 17.4%. The performance errors for each child using the covariate model are plotted in figure 3. The cross-validation resulted in an MAPE of −1.6% and an MAPE of 21%. The individual performance errors resulting from the cross-validation are presented in figure 4.

The mean context-sensitive half-times simulated from the newly derived pediatric parameters (covariate model) and from the original pharmacokinetic parameters used in CACI are displayed in figure 5. The context-sensitive half-time (CSHT) derived from another well-known set of adult fentanyl pharmacokinetic parameters is also displayed in the same figure. The CSHT is shorter for the pediatric patients, especially after infusions lasting more than 100 min. The simulated CSDTs for a 20%, 50%, and 80% decrement based on the covariate model (i.e., pharmacokinetic parameters adjusted for age and weight) for each child in the study is plotted in figure 6. To illustrate the differences in CSDT between the children studied and the original adult pharmacokinetic set, the mean CSDTs (20% and 50%) with their 95% confidence interval (simulated from the indi-
Table 2. Pharmacokinetic Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Original Adult Parameters (Mclain and Hug)</th>
<th>Derived Models</th>
<th>Covariate Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>V1 (L·kg⁻¹)</td>
<td>0.356³ weight</td>
<td>0.32 weight</td>
<td>0.43 (weight-19.8) + 5.8 [0.11, 1.1]</td>
</tr>
<tr>
<td>V2 (L·kg⁻¹ or L·yr⁻¹)</td>
<td>0.639³ weight</td>
<td>1.49 weight</td>
<td>6.2 (age-6.4) + 34.4 [1.7, 4.9]</td>
</tr>
<tr>
<td>V3 (L·kg⁻¹)</td>
<td>2.51³ weight</td>
<td>0.019³ weight</td>
<td>0.01 (weight-19.8) + 0.35 [0.004, 0.03]</td>
</tr>
<tr>
<td>Cl1 (L·kg⁻¹·min⁻¹)</td>
<td>0.0146³ weight</td>
<td>0.036³ weight</td>
<td>0.82 [0.12]</td>
</tr>
<tr>
<td>Cl2 (L·kg⁻¹·min⁻¹ or L·min⁻¹)</td>
<td>0.0659³ weight</td>
<td>2</td>
<td>-1.1</td>
</tr>
<tr>
<td>Cl3 (L·kg⁻¹·min⁻¹)</td>
<td>0.0502³ weight</td>
<td>23</td>
<td>17.4</td>
</tr>
<tr>
<td>MPE (%)</td>
<td>10.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAPE (%)</td>
<td>21.9</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values in brackets contain the standard error of the estimate (slope and intercept term). Cl1 = V1*K10, Cl2 = V1*K12, Cl3 = V1*K13. MPE = Median prediction error; MAPE = Median absolute prediction error.

individual [Bayesian] parameter estimates are plotted in figure 7.

**Discussion**

Computerized assisted continuous-infusion devices use previously determined pharmacokinetic parameters to infuse drugs to a targeted concentration. In this study, the use of adult pharmacokinetic data for fentanyl in a pediatric surgical population resulted in a modest positive bias between the predicted and measured values. The pharmacokinetic parameters derived from these pediatric patients was best fit by a two-compartment model with weight and age as covariates within the model. Simulations based on these pharmacokinetics showed that in children the CSHT is considerably shorter than indicated by simulations based on previously published adult pharmacokinetic parameters. We also demonstrated the variability in the duration of the CSHT among the children ages 2 to 11 y within this limited population.

To accurately determine pharmacokinetic parameters in pediatric patients, many patients are required, with children in each age range to encompass the developmental changes, from neonates and infants through adolescence. The need for such a large number of studies is compounded by the difficulties and ethical considerations in obtaining sufficient blood samples from children to determine bioavailability of agents. Despite the additional complexities, the pediatric age group remains poorly understood and the pharmacokinetic parameters for these cases need determination.

The calculation of the amount of fentanyl as the induction dose of fentanyl for infants, children and neonates is an important difference from adult. The weight reported by Niv et al. for a 70 kg fentanyl regimen varies from 70 to 30 μg/kg in patients and 200 g/kg in children. Routine analysis of serum concentrations is recommended in children. The pharmacokinetic parameters and the durations of the induction dose remain to be investigated. Although weight remains a key determinant, the authors showed that a prolonged induction dose (newborn to 60 kg) for sedation was adequately titrated age-relatedly (newborn to 60 kg) for analgesia.
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Fig. 5. Context-sensitive half-time (identical to the 50% context-sensitive decrement time) for the typical population values of the original adult kinetic set, the kinetics reported by Scott and colleagues, and the covariate model.

IT is considerably more difficult to estimate these parameters based on prospective pharmacokinetic data obtained in the duration of anesthesia for children aged 2 to 11 y within the clinical setting. To bypass the development of new infant/child kinetic parameters, McKnight and coworkers have used the kinetic data of adult patients to create a covariate model. In the present study, the authors have used the covariate model to generate context-sensitive half-times (CSHTs) for children for the purpose of preoperative planning.

The pharmacokinetics of fentanyl have been extensively studied in adults and children. However, the pharmacokinetics of fentanyl in children have been poorly understood. This study overcame these problems and described the disposition of fentanyl for a pediatric age range of 2 to 11 y in a relatively small population by using tools recently developed to help determine pharmacokinetic parameters. Similar studies could be performed in infants and neonates to describe the disposition of fentanyl in these age groups.

The calculations resulting from a single bolus dose of fentanyl as suggested by Singleton and coworkers in infants, children, and adults demonstrated pharmacokinetic differences among these age groups. In the study reported by those authors, the adults received 20 μg/kg fentanyl over 2 min, whereas the children received 30 μg/kg in the same period. However, the resulting serum concentrations were lowest in infants, intermediate in children, and highest in adults. The pharmacokinetic parameters were not derived from that study, but the authors suggested that either the clearance or volumes of distribution accounted for these differences. Although we studied a limited age range of 2 to 11 y, age remained a significant covariate in the model. The determination of the pharmacokinetics of fentanyl after a prolonged fentanyl infusion (ranging from 7 to 14 h) for sedation in mechanically ventilated children (newborn to 14 y) in the intensive care unit also demonstrated age-related differences. The children received a loading dose of 5 μg/kg followed by a mean infusion rate of 3.6 μg·kg⁻¹·h⁻¹. Children younger than 6 months and older than 6 y had an elimination clearance in the range of 480 ml·kg⁻¹·h⁻¹. The clearance in children between 6 months and 6 y of 1,131 ml·kg⁻¹·h⁻¹ was significantly larger. The children in this study also had various diseases (renal failure, liver disease, and so on) that are likely also to have influenced the pharmacokinetic parameters. The age-related alteration in the disposition of fentanyl probably reflects the interplay between maturational alterations in hepatic blood flow, development of the enzyme systems responsible for the metabolism of fentanyl, and body fat composition.

The original adult pharmacokinetic set performed in an acceptable manner in terms of MAPE (21.9%), but these parameters resulted in a prediction bias (10.4%; fig. 2). Because the original kinetics were based on a weight-proportional model, it is not surprising that the

Fig. 6. (Top) Context-sensitive decrement time (CSDT) for all the children using the covariate model. The individual lines result from the effect of different covariates (age and weight) on the model predictions. Three sets of CSDT indicate 80%, 50%, and 20% declines in plasma concentration after a steady-state infusion of the duration shown on the x axis. (Bottom) The same percentage decline CSDTs for the typical population values of the covariate model.

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derived pediatric weight-proportional model has a similar MAPE (23%) but a much smaller bias (2%). In exploring covariates in addition to weight, the generalized additive model (GAM) search suggested age (but no other covariates), leading to the covariate model that performed well in predicting the observed data (MAPE, 17.4%; MPE, -1.1%; fig. 3). In trying to validate the covariate model, we performed an internal cross-validation that allows a pseudo-prospective evaluation of the model. The ability of the collected "N-1" pharmacokinetic sets to predict the excluded children was acceptable (MAPE, 21%; MPE, -1.6%; fig. 4). The improvement in the prediction error from the original adult kinetic set and acceptable performance in the cross-validation suggests, but does not guarantee, that the model would perform reasonably well in a similar patient population. The parameters derived from a population will always perform better in that population than the parameters derived from a different population. Thus the parameters derived in this study need to be prospectively tested to confirm their utility in children.

Accurate pharmacokinetic parameters are not only important for their ability to determine infusion rates to target fentanyl concentrations in pediatric patients more accurately but may also help us to understand, through computer simulation of the CSHT, the likely rate at which plasma decline in drug concentration may occur. We closely examined the derived kinetics based on the individual (Bayesian) estimates for each child. The individual estimates represent our "best guess" of the pharmacokinetic variability from the children studied. The scope of this work does not allow a full explanation of individual Bayesian estimation (we refer the reader to a statistical text), but suffice it to say that Bayesian estimation differs from the "traditional" individual estimation (as reported in "standard two-stage" analysis) in that the Bayesian estimation accounts for the typical population values when deriving individual estimates. The result of using individual Bayesian estimation is that those individuals who differ markedly from the typical population model tend to "reigned in" toward the typical value; the degree to which the individual is "restrained" is a complex function based on how much information is known about the individual in question and the magnitude of the observed variability in the population.

To compare the pediatric population we studied with the typical adult predicted from our original kinetic set, we calculated the mean CSHT from the individual estimates from the pediatric population and plotted them together with the mean adult CSHT. In addition, we did the same procedure for a 20% CSDT (fig. 7). Depending on the percentage decrease in fentanyl concentration required, the average child's fentanyl concentration would decrease faster than the average adult after a steady-state infusion lasting more than 20 to 55 min.

When comparing the predicted recovery in our patient population with that of the typical adult (represented by the original adult kinetics), several issues arise. First, recovery is a combined pharmacokinetic and pharmacodynamic event. We did not assess a pharmacodynamic end point in this study, other than the

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Reference

1. Shaffer stereotyping fentanyl admixture.
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Achievement of “adequate” anesthesia as judged by the anesthesia provider. Second, we do not have a firm idea whether children have different analgesic requirements during the perioperative period compared with an adult population. Thus, we cannot exactly predict what decrease in plasma (and subsequently effect site) concentration (CSDT) would be needed in children. If both adults and children require a similar decrease in fentanyl concentration in the postanesthesia period, then we would expect the typical child to recover considerably faster than the typical adult, especially if infusions longer than 1 or 2 h are used (figs. 5 and 7). However, if children require a larger decrement in concentration compared with adults, the rapid pediatric recovery kinetics would be partially (or completely) negated. Nonetheless, the faster predicted recovery in the age range studied corresponds with our clinical impression that children recover from anesthesia more rapidly than adults do.

We tested an adult set of pharmacokinetics of fentanyl in children. The original pharmacokinetic parameters resulted in a consistent bias between the measured and predicted fentanyl concentrations. From these data, we derived a new pediatric fentanyl pharmacokinetic set that was described by a two-compartment model with age and weight as covariates within the model. These newly derived pharmacokinetic parameters corrected the consistent bias seen with the original adult pharmacokinetics and were tested by cross-validation. Thus we established an improved pharmacokinetic set for children having noncardiac surgery.

References


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