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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 y 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.[3-5] 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.[1,6] Computerized assisted continuous-infusion (CACI) devices use a set of pharmacokinetic parameters to deliver an intravenous drug to a target concentration.[7] These devices also record infusion rates so that it is possible from plasma sample data to determine the pharmacokinetic parameters that best describe the behavior of a drug in the population to

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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[8] 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 childrens' temperatures were maintained at more than 36°C. The children were assigned to two sequential groups of ten 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.[2,9,10] 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.[1,2] 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, Cl1[V1·K10], and Cl2[V1·K12]) and "constant c.v." variance model for the intraindividual 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,

§ An Excel 5.0 program written by Charles Minto and Thomas Schnider; available at anonymous FTP from pkpd.icon.palo-alto.med.va.gov or through the World Wide Web at http://pkpd.icon.palo-alto.med.va.gov.

‖ Written by Steven Shafer and available by anonymous FTP/URL at the locations noted the previous footnote.

Beal S, Scheiner L: NONMEM Project Group, University of California at San Francisco, 1992.

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

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[11] was then performed using SPlus for Windows†† (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 Cl1(V1 · K10), and no covariates on Cl2(V1 · K12).

We also performed an internal cross-validation in the manner described by Fiset and associates.[12] 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,[13] 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§§ was 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.

Table 1. Demographics

	Group A	Group B
Age (yr)	5.7 ± 2.6	6.6 ± 2.2
Weight (kg)	19.8 ± 7.1	20.9 ± 7.0
Height (cm)	117 ± 20	116 ± 20
Study duration (min)	232 ± 67	242 ± 80
Initial fentanyl measured (ng · ml−1)	10.2 ± 3.8	6.0 ± 3.1
Initial fentanyl predicted (ng · ml−1)	6.4 ± 2.9	4.2 ± 2.0

Values are mean ± SD.

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 h and 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.

The initial measured fentanyl concentrations in group A and group B were 10.2 ± 3.8 and 6 ± 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

†† Statistical Sciences, Seattle WA: StatSci, a division of MathSoft, 1994.

‡‡ Written by Scott Howell and available by request from the author at the following electronic mail address: howe1007@mc.duke.edu.

§§ The 50% CSDT is also known as the context-sensitive half-time (CSHT). When discussing only the 50% CSDT, we will use the CSHT notation.

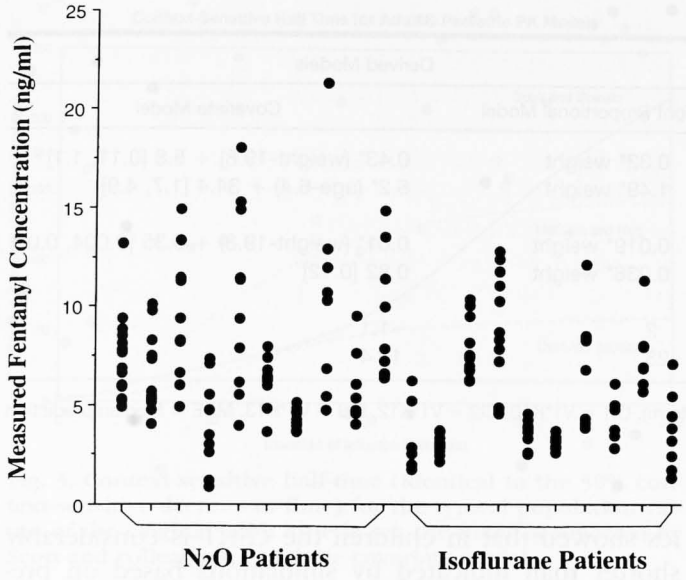

Fig. 1. A plot of the measured concentrations of fentanyl titrated to maintain adequate anesthesia in 20 children. The first ten patients received nitrous oxide, oxygen, and fentanyl *via* computerized assisted continuous infusion, and the second ten patients received nitrous oxide, oxygen with 0.5% isoflurane, and fentanyl delivered by computerized assisted continuous infusion.

group A. In group B, the median fentanyl values was 4.3 ng/ml (range, 1.3 to 12.8 ng/ml; *P* not significant). Figure 1 shows the plasma fentanyl concentrations for each patient. Two children in group B required naloxone at the end of the procedure, but the remaining 18 children breathed spontaneously at the end of their surgical procedures.

The measured plasma fentanyl concentrations were consistently greater than the CACI predicted plasma fentanyl concentrations. This resulted in a positive bias (median % performance error − MPE) of 10.4% and a 21.9% median % APE (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 *vs.* 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 Cl1(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 MPE of +2% and MAPE of 23% and the covariate model resulted in an MPE 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 MPE 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[14] is also displayed in the same figure. The CSHT is shorter for the pediatric set, especially after infusions lasting more than 100 min. The simulated CSDT 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-

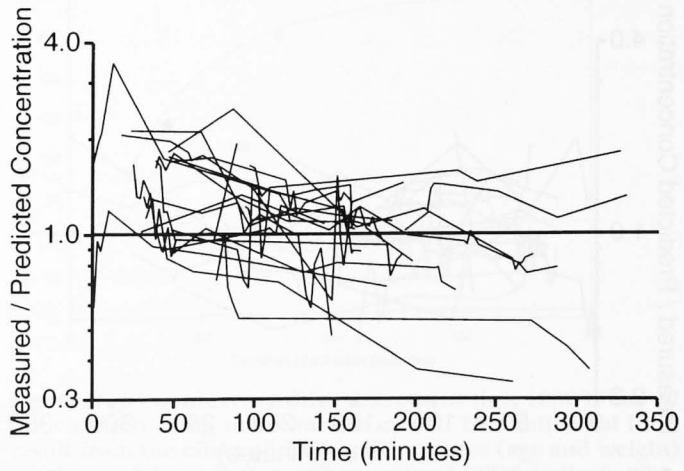

Fig. 2. Measured plasma concentration divided by predicted concentration from the original adult kinetic set. A perfect prediction would result in a measured/predicted value of 1 at all time points.

Table 2. Pharmacokinetic Parameters

Parameter	Original Adult Parameters (Mclain and Hug[8])	Derived Models	
		Weight Proportional Model	Covariate Model
V1 ($L \cdot kg^{-1}$)	0.356* weight	0.32* weight	0.43* (weight-19.8) + 5.8 [0.11, 1.1]
V2 ($L \cdot kg^{-1}$ or $L \cdot yr^{-1}$)	0.639* weight	1.49* weight	6.2* (age-6.4) + 34.4 [1.7, 4.9]
V3 ($L \cdot kg^{-1}$)	2.51* weight		
Cl1 ($L \cdot kg^{-1} \cdot min^{-1}$)	0.0146* weight	0.019* weight	0.01* (weight-19.8) + 0.35 [0.004, 0.03]
Cl2 ($L \cdot kg^{-1} \cdot min^{-1}$ or $L \cdot min^{-1}$)	0.0659* weight	0.036* weight	0.82 [0.12]
Cl3 ($L \cdot kg^{-1} \cdot min^{-1}$)	0.0502* weight		
MPE (%)	10.4	2	−1.1
MAPE (%)	21.9	23	17.4

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.

vidual [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.[15] The need for such a large number of studies is compounded by the difficulties and ethical considerations in obtaining sufficient blood samples from chil-

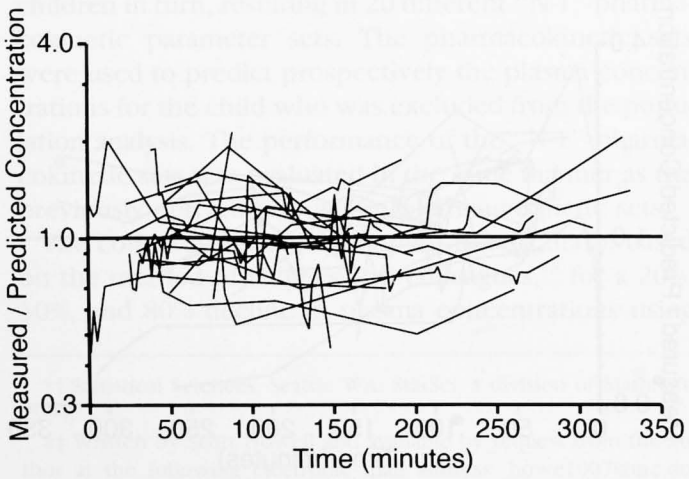

Fig. 3. Measured plasma concentration divided by predicted concentration from the model with two covariates. A perfect prediction would result in a measured/predicted value of 1 at all time points.

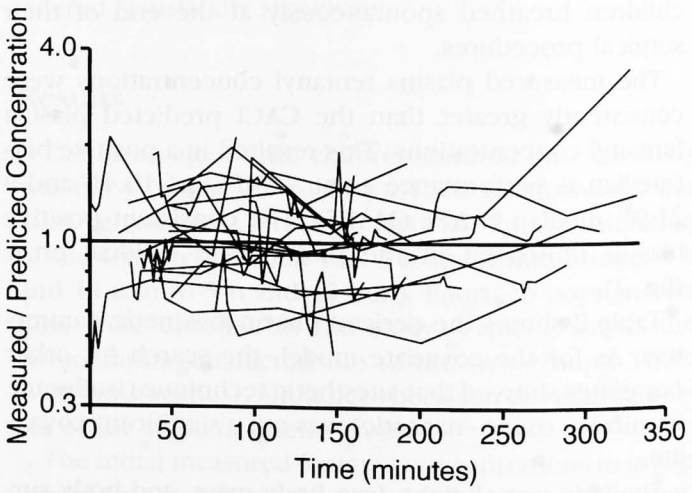

Fig. 4. Measured plasma concentration divided by predicted concentration from the cross-validation kinetic sets. Each line represents the measured concentrations from the excluded child divided by the "N-1" kinetic set prediction using the two-compartment covariate model (see text for complete description). A perfect prediction would result in a measured/predicted value of 1 at all time points.

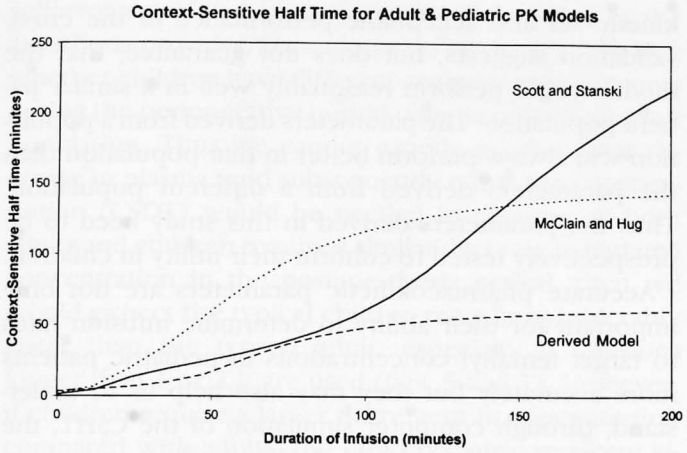

Fig. 5. Context-sensitive half-time (identical to the 50% context-sensitive decrement time) for the typical population values of the original adult kinetic set, the kinetics reported by Scott and colleagues,[14] and the covariate model.

dren to derive these pharmacokinetics. Fentanyl is commonly used in children to supplement other anesthetic agents. Despite its common use in pediatric patients, the pharmacokinetics of fentanyl in children remains 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[5] 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 144 h) for sedation in mechanically ventilated children (newborn to 14 y) in the intensive care unit also demonstrated age-related differences.[3] The children received a loading dose of 5 μg/kg followed by a mean infusion rate of 3.6 $\mu g \cdot kg^{-1} \cdot h^{-1}$. Children younger than 6 months and older than 6 y had an elimination clearance in the range of 480 $ml \cdot kg^{-1} \cdot h^{-1}$. The clearance in children between 6 months and 6 y of 1,131 $ml \cdot kg^{-1} \cdot h^{-1}$ 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

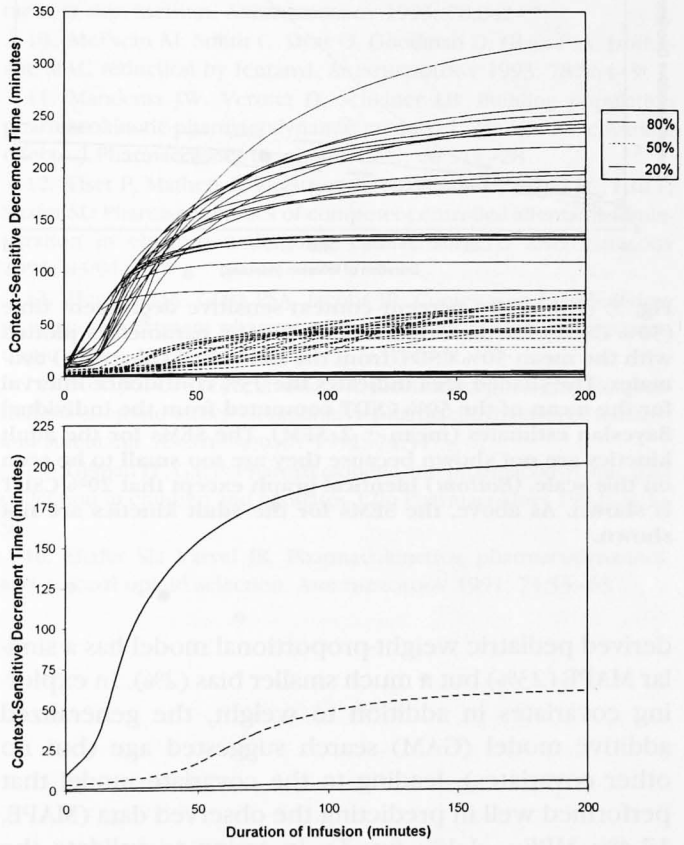

Fig. 6. (*Top*) Context-sensitive decrement time (CSDT) for all the children using the covariate model. The individual lines result from the effect of different covariates (age and weight) on the model predictions. Three sets of CSDT indicate 80%, 50%, and 20% declines in plasma concentration after a 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.

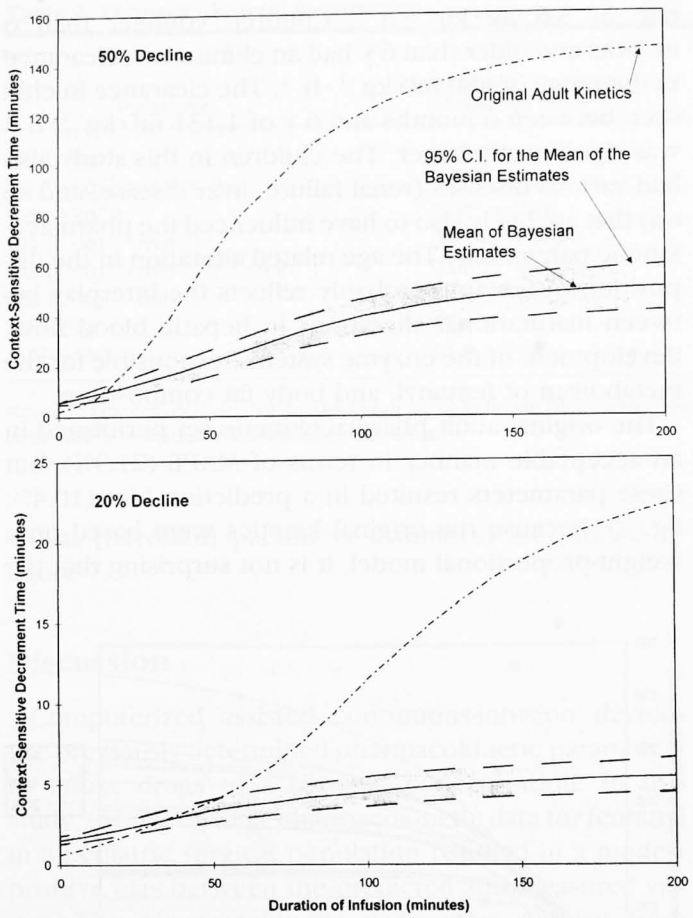

Fig. 7. (*Top*) Fifty percent context-sensitive decrement time (50% CSDT) for the original adult kinetic parameters plotted with the mean 50% CSDT from the individual (Bayesian) estimates. The shaded area indicates the 95% confidence interval for the mean of the 50% CSDT computed from the individual Bayesian estimates (mean ± 2·SEM). The SEMs for the adult kinetics are not shown because they are too small to be seen on this scale. (*Bottom*) Identical graph except that 20% CSDT is shown. As above, the SEMs for the adult kinetics are not shown.

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.[12] 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 performance 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 they may also help us to understand, through computer simulation of the CSHT, the likely rate at which plasma decline in drug concentration may occur.[13,16] 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 populations 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

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.

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