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## Pharmacokinetics of Computer-controlled Alfentanil Administration in Children Undergoing Cardiac Surgery

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**Background:** Cardiopulmonary bypass (CPB) induces changes in the pharmacokinetics of drugs. The purpose of this study was to model the pharmacokinetics of alfentanil in children undergoing cardiac surgery to provide accurate dosage titration intraoperatively as well as in the postoperative period.

**Methods:** Fourteen children (aged 3 months to 8 yr) undergoing cardiac surgery with CPB were administered alfentanil via a computer-controlled infusion pump. During surgery, the computer-controlled infusion pump was set to target plasma alfentanil concentrations of 500–2500 µg/ml. After surgery, the computer-controlled infusion pump was set to target plasma concentrations of 200–500 µg/ml. Parameters for children previously published by Goresky *et al.* were programmed into the device. Arterial blood samples were taken throughout the infusion. Plasma samples were assayed by radioimmunoassay. Alfentanil pharmacokinetics were estimated using a pooled-data approach with a simple weight-proportional,

three-compartment mamillary model with parameters expressed in volumes and clearances as well as a CPB-adjusted three-compartment model in which the parameters were allowed to change before, during, and after CPB. The accuracy of the three models was compared using cross-validation.

**Results:** Plasma alfentanil concentrations during computer-controlled infusion pump administration exceeded target concentrations for the first 10 min of drug administration and from 300 min to the end of the study. The median absolute performance error was 33%. Pharmacokinetic modeling estimated a set of parameters for a simple three-compartment model with a median absolute weighted residual of 18.4%. CPB-adjusted model nominally decreased the median absolute weighted residual to 17.0%. The performance of these models as measured by cross-validation performance was 18.9% median absolute performance error for the simple model and 18.4% median absolute performance error for the CPB-adjusted model. Parameters for the simple three-compartment model are:  $V_1 = 19.2 \text{ ml} \cdot \text{kg}^{-1}$ ;  $V_2 = 99 \text{ ml} \cdot \text{kg}^{-1}$ ;  $V_3 = 2344 \text{ ml} \cdot \text{kg}^{-1}$ ;  $Cl_1 = 2.5 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ;  $Cl_2 = 38 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ; and  $Cl_3 = 1 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ . In the CPB-adjusted model  $V_1$ ,  $V_2$ , and  $Cl_1$  changed with the onset of CPB. After CPB,  $V_1$  and  $Cl_1$  returned to the initial values, while  $V_2$  was described by a third value.

**Conclusions:** The population pharmacokinetics of alfentanil in children undergoing cardiac surgery were well described by both a simple weight-proportional, three-compartment model and a weight-proportional, CPB-adjusted three-compartment model. Cross-validation estimated an expected median inaccuracy of approximately 18–20% with the estimated models in identical experimental circumstances. The flexible CPB-adjusted pharmacokinetic model could be used for modeling any drug with linear pharmacokinetics given in the context of CPB. (Key words: Anesthesia, pediatric; cardiac; intravenous. Equipment: cardiopulmonary bypass; computer-controlled infusion pump. Pharmacokinetics: alfentanil. Statistics: cross-validation.)

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CHILDREN often require overnight ventilation of their lungs after cardiac surgery. During this interval of 12–18 hr, a child may become agitated if inadequately sedated. Agitation increases blood pressure and heart rate, possibly posing a risk to the child. In our pediatric intensive care unit, various combinations of morphine, midazolam, and fentanyl infusions were tried during pa-

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tients' first postoperative nights to provide adequate sedation. Children who were adequately sedated the night after surgery were often excessively sedated the next morning, necessitating continued controlled ventilation.

We attempted to solve this clinical dilemma by sedating children using a computer-controlled infusion of alfentanil. Alfentanil was chosen because the pharmacokinetics in adults suggested that after a prolonged infusion, *i.e.*, longer than 8 hr, recovery characteristics were the most favorable of all available opioids.<sup>1</sup> Alfentanil administered by computer-controlled infusion pump (CCIP) was the primary anesthetic during surgery and provided postoperative analgesia and sedation overnight after surgery.

Many investigators have described the influence of cardiopulmonary bypass (CPB) on the plasma concentrations of drugs used during anesthesia.<sup>2-8</sup> Most of these studies have described the concentrations over time, without developing quantitative pharmacokinetic models that can be used for improved drug administration during and after CPB. The purpose of this study was to model the pharmacokinetics of alfentanil in children undergoing cardiac surgery, and to develop a pharmacokinetic model appropriate for both intraoperative titration and postoperative sedation.

## Materials and Methods

### Clinical Study

After Institutional Review Board approval of the protocol, 14 children, aged 3 months to 8 yr, undergoing cardiac surgery with the use of CPB were studied with the written informed consent of their parents. Of the 14 patients, 9 were younger than 1 yr, and 5 were aged 1-8 yr (table 1). The opioid alfentanil was infused with a computer-controlled infusion pump (CCIP), programmed with parameters obtained from normal healthy children<sup>9</sup> to maintain a constant plasma alfentanil target concentration. Anesthesia was induced with halothane by mask. After induction of anesthesia, the children received alfentanil for maintenance of anesthesia supplemented as needed with isoflurane 0.5-1.0% to provide hemodynamic stability. Vecuronium was administered to provide muscle relaxation. The patients received alfentanil by CCIP for up to 24 hr for postoperative analgesia and sedation. If agitation could not be controlled with alfentanil alone supplemental midazolam was administered.

The alfentanil was titrated as follows. The initial alfentanil target plasma concentration was 500 ng/ml,

**Table 1. Demographic and Clinical Data for the 14 Children Studied**

Patient No.	Age (mo)	Weight (kg)	Diagnosis	Prime solution Total Volume (ml)	Time on CPB (min)
1	4	5.7	TET	600	86
2	12	6.11	ASD	675	26
3	3	3.96	AV canal	650	95
4	11	6.7	AV canal	650	100
5	12.5	8	VSD	555	92
6	7	6.95	VSD	760	37
7	17	9	VSD	100	56
8	41	14.5	ASD	800	27
9	7	6.1	VSD	650	58
10	4	4.8	TET	700	71
11	24	12.3	TET	850	81
12	101	25.5	VSD	1155	45
13	4.5	6.55	TET	900	83
14	4.5	6.3	TET	950	92

ASD = atrial septal defect; VSD = ventricular septal defect; TET = tetralogy of Fallot; PVS = pulmonary vein stenosis; CPB = cardiopulmonary bypass.

which was maintained until just before sternotomy, when it was increased to 1000 ng/ml. Immediately before the initiation of cardiopulmonary bypass the target concentration was increased to 1500 ng/ml. If the child responded hemodynamically to sternotomy or other surgical stimulation the target concentration was increased by 250-500 ng/ml. The highest target alfentanil concentration required was 2500 ng/ml. After termination of CPB the concentration was decreased to 1000 ng/ml, and then further decreased as clinically tolerated. In the intensive care unit, the target concentration was decreased to 500 ng/ml and from there further decreased as tolerated. The morning after surgery, the alfentanil infusion was discontinued and the patient's trachea was extubated.

Twenty to forty one-milliliter arterial blood samples were drawn from each child for plasma alfentanil determination. Samples were drawn at 1, 2, 6, 10, 15, 20, 22, 25, 30, 45, and 60 min after initiation of the CCIP, 1, 3, 4, 8, 12, 17, 32, 47, and 60 min after the onset of CPB, and 5, 10, 15, 20, 25, and 30 min after termination of CPB. In the intensive care unit, samples were taken every 15 min for the first hour, and then every hour for a total period of 24 hr. After excluding the nearly random sample (explained in results section) taken 1 min after the onset of CPB, the total number of samples was 478. Plasma samples were assayed by radioimmunoassay, with a lower quantitation limit

of 4.4 ng/ml, and a between-day variation of less than 5%.<sup>10</sup>

#### Computer-controlled Infusion Pump

The CCIP administered an exponentially declining infusion, adjusted every 10 s to maintain a constant plasma alfentanil concentration. The parameters for the pharmacokinetic model in the CCIP were taken from a previous study of alfentanil pharmacokinetics in children by Goresky and colleagues<sup>9</sup> in which the authors derived two different sets of pharmacokinetics for children younger and older than 1 yr of age based on a two-compartment model. The computer created a disk file with a record of each 10-s infusion. This disk file provided the detailed infusion record used by MKMODEL\*\* in the pharmacokinetic modeling.

The CCIP consisted of an 80286 portable computer running MS-DOS connected to a Harvard Pump 22 (Harvard Apparatus, Boston, MA). The CCIP ran the software program STANPUMP. The CCIP hardware and software have been described in detail previously.<sup>11-13</sup>

The performance of the CCIP was measured using the performance error (PE), defined as:

$$PE = \frac{M - P}{P} \times 100\%$$

where M is the measured concentration and P is the concentration predicted by the pump. The predicted concentration was the same as the target plasma concentration except immediately after requesting a lower target concentration, when the infusion stopped while the predicted concentration declined to the desired target concentration. The overall performance of the CCIP was described using the median absolute performance error, MDAPE, defined as:

$$MDAPE = \text{median} (|PE_1|, |PE_2|, \dots, |PE_n|)$$

for n = total number of observations.

The bias in the performance of the CCIP was described using the median performance error, MDPE, defined as:

median performance error

$$= \text{median} (PE_1, PE_2, \dots, PE_n)$$

\*\* Available from the author, Nicholas Holford, M.Sc., M.R.C.P. (U.K.), F.R.A.C.P., Department of Pharmacology and Clinical Pharmacology, School of Medicine, University of Auckland, Private Bag, Auckland, New Zealand.

#### Pharmacokinetic Analysis

**Simple Pharmacokinetic Model.** Two- and three-compartment mamillary models with parameters expressed in volumes and clearances were estimated using the nonlinear regression program MKMODEL.\*\* Data from the whole study period were included and the use of CPB was not a consideration. The log-likelihood was used as an objective function to optimize parameters as well as to validate the choice of a three-compartment over a two-compartment model.

**CPB-adjusted Pharmacokinetic Model.** We defined the pre-CPB period as starting at the beginning of the alfentanil infusion and continuing through the moment the bypass pump was started. The CPB period was the interval between when the bypass pump was started and when it was turned off. The post-CPB period extended from the discontinuation of bypass until the end of blood sampling. Overnight sedation was provided by alfentanil, so the post-CPB period extended for many hours after the end of surgery.

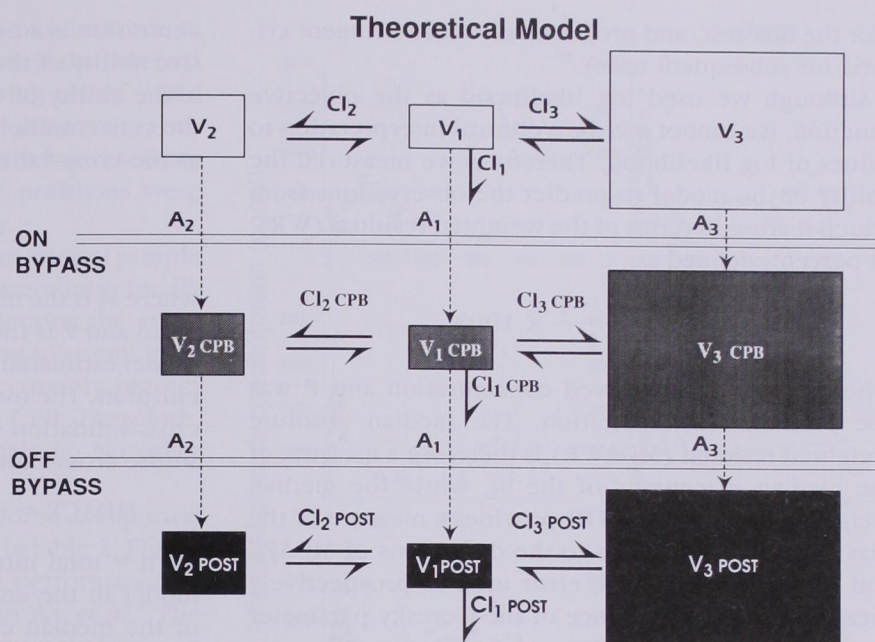
We assumed that during each period the pharmacokinetics were linear, and were best described by a triexponential disposition function:

$$UDF = \sum_{i=1}^n Ae^{-\alpha t}$$

where UDF = unit disposition function and n = 3 for a three-compartment model. We interpreted the disposition function within each time period as representing the volumes and clearances of a three-compartment mamillary model, as shown in figure 1. At the time of each transition (*i.e.*, pre-CPB to CPB and CPB to post-CPB), we assumed that the amount of drug in the two peripheral compartments did not change. However, both the volume of the compartment and the associated intercompartmental clearance were permitted to change with the transition on or off CPB.

The central compartment was accounted for in a different manner, reflecting the influence of the bypass reservoir. At the onset of CPB, V<sub>1</sub> was handled just as the volume was handled for the other compartments. The amount of drug in the central compartment did not change, but the volume was allowed to change acutely, producing a step change in the measured concentration. This acute volume change was intended to model the sudden hemodilution produced by addition of the pump prime and CPB reservoir volume to the patient's circulating blood volume. At the conclusion of CPB, we assumed that the concentration in the central compartment remained constant, but that the vol-

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**Fig. 1.** Theoretical cardiopulmonary-bypass-adjusted pharmacokinetic model. The parameters of the multi-compartmental model are allowed to change in the three different periods delimited by onset and weaning from cardiopulmonary bypass.

ume acutely decreased. This permitted loss of alfentanil to the bypass pump when CPB was terminated. Thus, the amount of drug in  $V_1$  was allowed to change acutely at the end of bypass, whereas the amounts in the other compartments were not permitted to change acutely at the end of bypass.

Thus, both volumes and clearances were assumed to change acutely with the onset and offset of CPB, but the amounts of drug in the compartments were assumed not to change, except for the amount in the central compartment at the conclusion of CPB. We also assumed that the physiologic changes in each period were sudden and persisted for the whole specific period. Our assumptions are only approximations. The extent to which they permitted us to describe the alfentanil concentrations observed with the onset and offset of CPB measure how well these simple modeling assumptions accounted for the influence of the true physiologic changes on plasma alfentanil concentration.

MKMODEL was used for the nonlinear regression analysis and was programmed to simultaneously fit up to 18 parameters: 3 volumes and 3 clearances for each time interval (pre-CPB, during CPB, and post-CPB). The model was developed by starting with the assumption that the three volumes and three clearances did not change with the transition on and off CPB. Individual volumes and clearance terms, reflecting the changes with the transition, were then individually added to

the model. If the log likelihood increased by 2, then the additional parameter was considered justified.<sup>14</sup> Additionally, before we added a new volume and clearance term describing the pharmacokinetics in the post-bypass period, we investigated the performance of the volume or clearance parameters from the two previous intervals (*i.e.*, pre-CPB or during CPB) to see if either term adequately described the data (as measured by log likelihood). In this way, a parsimonious model was developed which described with as few terms as possible the pharmacokinetic changes associated with CPB.

The simple and CPB-adjusted pharmacokinetic models were estimated by fitting the parameters of the model to the data from all children simultaneously (naive pooled data approach), although individual covariates and infusion profiles were included in the model.<sup>15,16</sup> The errors tended to be proportional to the predicted concentration, so we used the constant coefficient of variation model for the variance:

$$\text{Variance} = \sigma P^2$$

where  $\sigma$  is the variance scale parameter set so the sum of the weighted squared errors equals the number of observations and  $P$  is the predicted concentration. Log likelihood was the objective function. The statistical significance of adding a new parameter to the existing model was tested and the new model was considered better if log likelihood increased by approximately 2

(for the first test, and progressively more stringent criteria for subsequent tests).<sup>17</sup>

Although we used log likelihood as the objective function, we cannot ascribe a clinical interpretation to values of log likelihood. Therefore, we measured the ability of the model to predict the observations from which it arose in terms of the weighted residual (WR), in percent, defined as:

$$WR = \frac{M - P}{P} \times 100\%,$$

where M was the observed concentration and P was the predicted concentration. The median absolute weighted residual (MDAWR) is therefore a measure of the median inaccuracy of the fit, while the median weighted residual (MDWR) provides a measure of the bias of the fit. Analogous to the definitions of MDAPE and median performance error used to prospectively measure CCIP performance of the Goresky parameter sets,<sup>9</sup> MDAWR and MDWR are defined as:

$$MDAWR = \text{median} (|WR_1|, |WR_2|, \dots, |WR_n|)$$

and

$$MDWR = \text{median} (WR_1, WR_2, \dots, WR_n)$$

The weighted residual is a retrospective analysis of the quality of the fit, whereas the performance error is a prospective analysis of CCIP performance. The measures of error are identical in form to permit estimation of the improvement in performance that might be expected from the derived pharmacokinetic parameters. Because some of the random error invariably is described by the estimated pharmacokinetic parameters, the weighted residuals overestimate the expected accuracy of the pharmacokinetic parameters.

**Cross-validation.** We did not have the opportunity to test the derived pharmacokinetic models prospectively. Therefore, we estimated how well the new pharmacokinetic models were likely to perform in prospective tests using cross-validation.<sup>18</sup> We cross-validated both the simple three-compartment model and the CPB-adjusted model. To perform the cross-validation, we re-estimated the model parameters 14 times. In each re-estimation step, the data from a single child were excluded from the analysis. We then analyzed, for each excluded child, how well the submodel estimated from the other 13 children predicted the observations in the excluded child. Because the child's data were not used to develop the model, the difference between the model prediction and the observed con-

centration is a nearly unbiased estimate of the predictive ability of the model.

The ability of each of the 14 sub-models to predict the concentrations in the excluded child was measured as the cross-validation error (CV), defined as:

$$CV = \frac{M - P}{P} \times 100\%,$$

where M is the measured concentration in the excluded child and P is the concentration predicted by the sub-model estimated from the observations in the other 13 children. The overall performance of the model in the cross-validation was described using the median absolute cross-validation error, MDACV, defined as:

$$MDACV = \text{median} (|CV_1|, |CV_2|, \dots, |CV_n|)$$

for n = total number of observations. The bias of the model in the cross-validation was measured in terms of the median cross-validation error, MDCV, defined as:

$$MDCV = \text{median} (CV_1, CV_2, \dots, CV_n)$$

We also graphed the performance errors in the cross-validation study for each of the 14 children, displaying for each child the error in predicting that child's observations using the submodel calculated from the other 13 children.

Residual errors are favorably biased, in that they overestimate the predictive ability of the model by incorporating some of the noise in the observations into the model parameters. The "leave-one-out" approach to cross-validation provides an approximately unbiased estimator of the expected error between the model prediction and the measured concentrations.<sup>19</sup> The bias occurs because the individual submodels in the "leave-one-out" approach are developed with one less individual than the final model, and hence are less accurate than the final model. Thus, the predictive ability of the final model would be expected to be slightly better (under identical experimental circumstances) than the predictive ability calculated using cross-validation. In other words, cross-validation is a conservative measurement of the expected error in prediction.

## Results

Alfentanil infusion provided clinically unremarkable anesthesia in the 14 children. All children had their trachea extubated on the first postoperative day. The

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hardware performed well except for one instance in which the surgical electrocautery erased the internal memory of the Harvard Pump 22, causing a brief, rapid infusion of alfentanil. The STANPUMP software was altered to automatically detect and recover from memory loss in the Harvard Pump. No other problems were observed.

The alfentanil concentration from the arterial sample gathered 1 min after the onset of CPB was almost totally random (range 27.9–705 ng/ml) reflecting the acute dilution from the bypass pump priming solution. Even the CPB-adjusted model could not accurately predict the sample drawn 1 min after starting CPB. Therefore, this sample was deleted from the analysis. No other observations were deleted.

Pharmacokinetic parameters for children as reported by Goresky and colleagues<sup>9</sup> are shown in table 2. Figure 2 (top) shows the median and worst performance of the pharmacokinetics reported by Goresky *et al.*<sup>9</sup> The performance errors for all 14 children are shown in figure 3 (top). The prospective testing of Goresky's pharmacokinetics with the CCIP yielded a median performance error (bias) of +24% in children younger

Table 2. Goresky Pharmacokinetic Parameters for Children\*

	<1 Year Old	>1 Year Old
Volumes (ml · kg <sup>-1</sup> )		
V <sub>1</sub>	246	213
V <sub>2</sub>	205	190
V <sub>dss</sub>	451	403
Clearances (ml · kg <sup>-1</sup> · min <sup>-1</sup> )		
Cl <sub>1</sub>	8.86	7.84
Cl <sub>2</sub>	3.69	3.58
Fractional coefficients (unitless)		
A	0.85	0.85
B	0.15	0.15
Exponents (min <sup>-1</sup> )		
α	0.0578	0.0610
β	0.0112	0.0113
Half-lives (min)		
t <sub>1/2</sub> α	12	11
t <sub>1/2</sub> β	62	61
Micro-rate constants (min <sup>-1</sup> )		
k <sub>10</sub>	0.036	0.037
k <sub>12</sub>	0.015	0.017
k <sub>21</sub>	0.018	0.037
MDPE (%)	+24	-7
MDAPE (%)	34	32

MDPE = median performance error, MDAPE = median absolute performance error.

\* As implemented into the STANPUMP program.

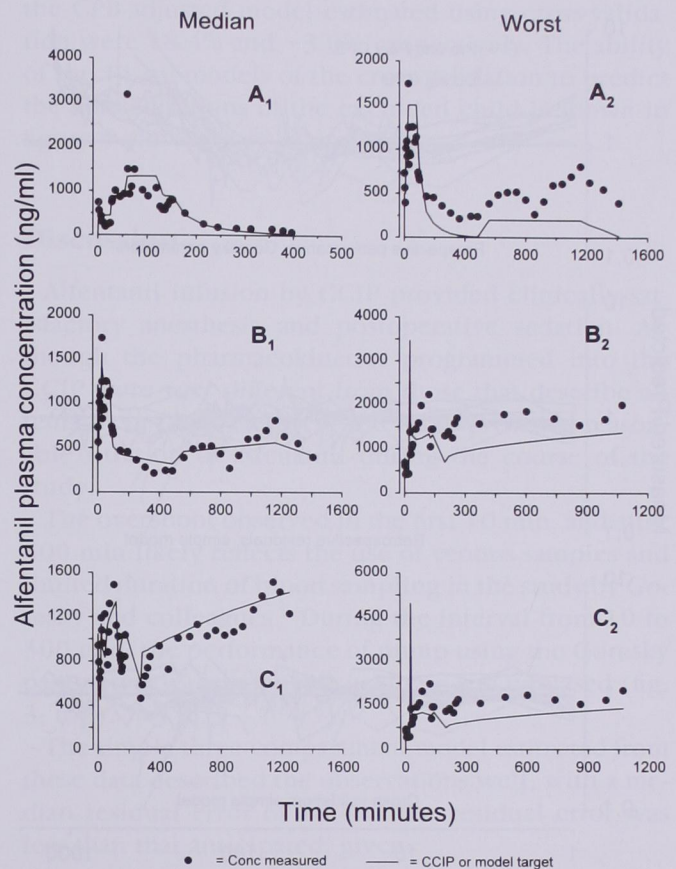


Fig. 2. Median and worst prediction ability based on Goresky's pharmacokinetics (A<sub>1</sub> and A<sub>2</sub>), the simple three-compartment model (B<sub>1</sub> and B<sub>2</sub>) and the cardiopulmonary-bypass-adjusted three-compartment model (C<sub>1</sub> and C<sub>2</sub>).

than 1 yr, and of -7% in children older than 1 yr. The MDAPE (inaccuracy) was 34% in children younger than 1 yr, and 32% in children older than 1 yr. Before 10 min elapsed, the CCIP consistently produced an overshoot of the target concentration. An overshoot also was observed after 300 min, and this error increased over time (fig. 3, top). Examination of the performance errors from 10 to 300 min suggests that within these time points the Goresky model was more accurate than at earlier or later times. The MDAPE during the interval from 10 to 300 min was 27.8% in children younger than 1 yr, and was 24.1% in children older than 1 yr.

Table 3 shows the pharmacokinetics for the simple three-compartment model derived from the pooled data analysis. The clearance of alfentanil in our children was approximately 30% of the clearance estimated by Goresky and colleagues.<sup>9</sup> The V<sub>dss</sub> in our population was nearly fivefold larger (451 ml · kg<sup>-1</sup> (<1 yr) and

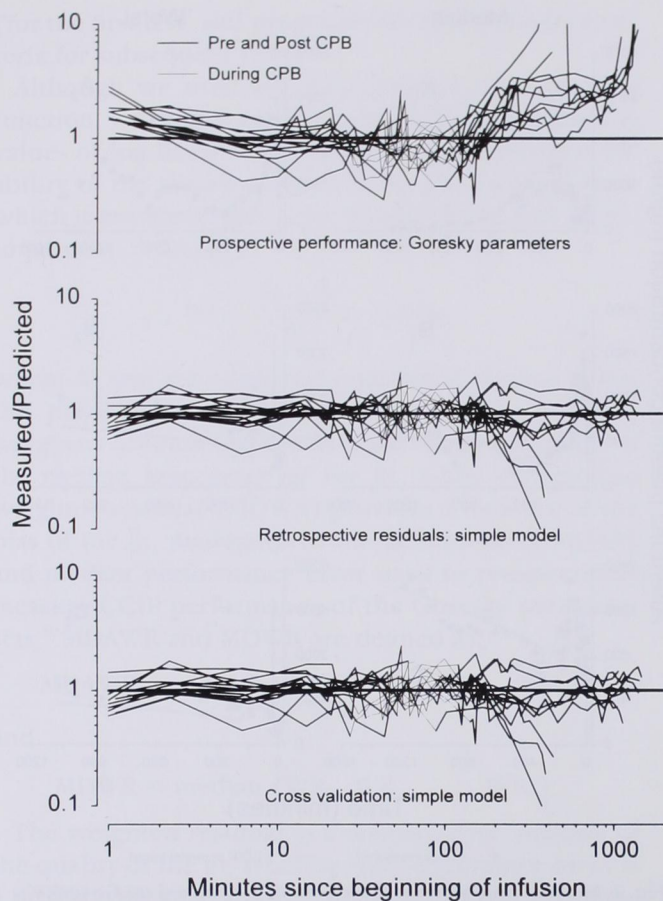


Fig. 3. The top panel shows the performance errors over time in the 14 children observed prospectively with a computer-controlled infusion pump infusion based on Goresky's pharmacokinetics. The middle panel shows the weighted residual errors over time in the same 14 children, based on the simple three-compartment model of alfentanil. The bottom panel shows the cross-validation errors of the 14 submodels of the three-compartment model in the child excluded from each submodel. The errors on the Y axis are 1 plus the error term as described in the text. The addition of 1 is required to graph the errors on a logarithmic axis.

403 ml · kg<sup>-1</sup> (>1 yr) vs. 2462 ml · kg<sup>-1</sup>). The reduced clearance and larger V<sub>dss</sub> accounted for the slower elimination half-life of alfentanil (799 vs. 60 min) observed in this study. The median and worst fits for the three-compartment model are shown in figure 2 (middle, B<sub>1</sub> and B<sub>2</sub>). Figure 3 (middle) shows the weighted residuals for the simple three-compartment model for all 14 children. The parameters estimated for a simple three-compartment model described the data well, with an MDAWR of 18.4% and an MDWR of -3.7%. The MDACV and MDCV estimated using cross-validation were 18.9% and -3.6%, respectively. The ability of the

14 submodels of the cross-validation to predict the concentrations in the excluded child is shown in figure 3 (lower).

Table 4 shows the volumes and clearances of the CPB-adjusted model of alfentanil. The data supported only changing 3 parameters with the onset of CPB: V<sub>1</sub>, V<sub>2</sub>, and Cl<sub>2</sub>. After termination of CPB, V<sub>1</sub> and Cl<sub>2</sub> returned to their initial values, whereas V<sub>2</sub> increased slightly. The CPB-adjusted model was favored over the simple three-compartment model by an increase in log likelihood of 18. Figure 4 shows the optimal CPB-adjusted model.

Table 3. Pharmacokinetic Parameters for the Simple Three-compartment Model

Estimated parameters	
Volumes (ml · kg <sup>-1</sup> )	
V <sub>1</sub>	19.2
V <sub>2</sub>	99
V <sub>3</sub>	2,344
Clearance (ml · kg <sup>-1</sup> · min <sup>-1</sup> )	
Cl <sub>1</sub>	2.5
Cl <sub>2</sub>	38
Cl <sub>3</sub>	15
Parameters calculated from volumes and clearances	
V <sub>dss</sub> (ml/kg)	2462
Fractional coefficients (unitless)	
A	0.91
B	0.08
C	0.01
Exponents (min <sup>-1</sup> )	
α	3.13
β	0.114
γ	0.0008
Half-lives (min)	
t <sub>1/2</sub> α	0.22
t <sub>1/2</sub> β	6.1
t <sub>1/2</sub> γ	799
Micro-rate constants (min <sup>-1</sup> )	
K <sub>10</sub>	0.128
K <sub>12</sub>	1.96
K <sub>13</sub>	0.779
k <sub>21</sub>	0.380
k <sub>31</sub>	0.00638
Weighted residuals (retrospective)	
MDAWR	18.4
MDWR	-3.7
Cross-validation measures (estimate of prospective performance) (%)	
MDACV	18.9
MDCV	-3.6

MDACV = median absolute cross-validation error; MDCV = median cross-validation error; MDAWR = median absolute weighted residual; MDWR = median weighted residual.

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**Table 4. Estimated Pharmacokinetic Parameters from the Optimal Weight Proportional, Cardiopulmonary Bypass-adjusted Three-compartment Model**

Prebypass	
Volumes (ml · kg <sup>-1</sup> )	
V <sub>1</sub>	9.6
V <sub>2</sub>	80
V <sub>3</sub>	2,260
Clearances (ml · kg <sup>-1</sup> · min <sup>-1</sup> )	
Cl <sub>1</sub>	2.4
Cl <sub>2</sub>	28
Cl <sub>3</sub>	15
With onset of CPB	
Volumes (ml · kg <sup>-1</sup> )	
V <sub>1</sub>	20*
V <sub>2</sub>	142*
V <sub>3</sub>	2,260
Clearances (ml · kg <sup>-1</sup> · min <sup>-1</sup> )	
Cl <sub>1</sub>	2.4
Cl <sub>2</sub>	16*
Cl <sub>3</sub>	15
With offset of CPB	
Volumes (ml · kg <sup>-1</sup> )	
V <sub>1</sub>	9.6†
V <sub>2</sub>	192‡
V <sub>3</sub>	2,260
Clearances (ml · kg <sup>-1</sup> · min <sup>-1</sup> )	
Cl <sub>1</sub>	2.4
Cl <sub>2</sub>	28†
Cl <sub>3</sub>	15
Improvement in log likelihood from simple model: 18	
Weighted residuals (retrospective) (%)	
MDAWR	17.0
MDWR	-2.3
Cross-validation measures (%)	
MDACV	18.4
MDCV	-3.0

CPB = cardiopulmonary bypass; MDAWR = median absolute weighted residual; MDWR = median weighted residual; MDACV = median absolute cross validation error; MDCV = median cross validation error.

\* Parameter change from prebypass.

† Returns postbypass to the prebypass value.

‡ Parameter changes postbypass to a new value.

The parameters estimated for the CPB-adjusted model offered a nominally better description of the observations than the simple three-compartment model, with an MDAWR of 17.0% and an MDWR of -2.3%. Figure 2 (lower) shows the median and worst performance of the CPB-adjusted pharmacokinetic model. The weighted residuals over time for all children are shown in figure 5 (top). Comparison of this with figure 3 (middle) confirms that the CPB-adjusted model offered little improvement in predictive accuracy to the simple three-compartment model. The MDACV and MDCV of

the CPB-adjusted model estimated using cross-validation were 18.4% and -3.0%, respectively. The ability of the 14 submodels of the cross-validation to predict the concentrations of the excluded child is shown in figure 5 (lower).

## Discussion

Alfentanil infusion by CCIP provided clinically satisfactory anesthesia and postoperative sedation. Although the pharmacokinetics programmed into the CCIP were very different from those that describe alfentanil in these children, the CCIP provided reasonable titration of alfentanil during the course of the study.

The overshoot observed in the first 10 min, and after 300 min likely reflects the use of venous samples and limited duration of blood sampling in the study by Goresky and colleagues.<sup>9</sup> During the interval from 10 to 300 min, the performance of pump using the Goresky parameters was reasonably accurate and unbiased (fig. 3, top).

The simple three-compartment model estimated from these data described the observations well, with a median residual error of 18.4%. The residual error was less than that anticipated, given:

1. the underlying physiologic perturbations associated with anesthesia, cardiac surgery, and cardiopulmonary bypass<sup>20,21</sup>
2. the presence of congenital heart defects, arteriovenous shunts, and various degrees of heart failure
3. target plasma alfentanil concentrations ranging from 200 to 2500 ng/ml
4. an age range from 3 months to 8 yr

Despite the accumulated influence of these sources of variability the pharmacokinetic model accurately predicted the observed concentrations both in retrospective measures of residual error and in the cross-validation.

The CPB-adjusted model resulted in an improved MDAWR from 18.4% to 17.0%. This represents a reduction in the residual error of approximately 8%. This is only a modest improvement, primarily because of the good fit to the data with the simple model. The CPB-adjusted model resulted in improvement in the estimation of 54% of the observations.

The CPB-adjusted model reduced the magnitude of the outliers, so that the range from the 10% error to



the 90% error decreased from  $-37.4$ – $40.1\%$  with the simple model to  $-32.1$ – $39.2\%$  with the CPB-adjusted model. Outliers might be associated with the greatest risk of underdose or overdose, and thus the CPB-adjusted model might result in a clinical benefit in some children although the improvement for the typical individual would be small. Figure 5 shows that the CPB-adjusted model leaves three obvious outliers in separate children. In two of those children, the outlier represents a single terminal data point. The other child has many misspecified data points at the end of the sampling period. We have examined the characteristics of these three children and could not identify any methodologic or physiologic reasons to explain the misspecification.

In a previous study of alfentanil administration by CCIP, the MDAPE ranged from 17% to 55% depending on the pharmacokinetic parameters used.<sup>22</sup> Using the nonparametric plasma efflux approach, Crankshaw *et al.* were able to obtain an MDAPE of 11% during a 1 hr infusion of alfentanil designed to maintain a single target plasma concentration.<sup>23</sup> Our MDAPE of 17.4% is not as accurate as the results obtained by Crankshaw, but compares favorably to the previous studies using pharmacokinetically based target-controlled infusions.

The purpose of this study was to prospectively test the pharmacokinetics reported by Goresky<sup>9</sup> and to develop an improved model relating dose to concentration. The physiology responsible for drug elimination

from the plasma are processes of systemic clearance and intercompartmental clearance into anatomic volumes. Therefore, it is intuitively satisfying to report the parameters of the model in terms of volumes and clearance, in the belief that the model may reflect the underlying physiology. However, such models, when solely based on plasma drug concentrations, are only a mathematical transformation of the unit disposition function of the drug (*i.e.*, the impulse response function). It is likely that the volumes and clearances do not correspond to specific anatomic structures or functions.

The increase in  $V_1$  we observed during CPB was likely caused by the addition of the pump volume to the initial mixing volume between the venous infusion site and the arterial sampling site. We found no correlation between the amount of pump prime and the residual errors. The CPB model did not show changes in systemic clearance ( $Cl_1$ ) during bypass, a surprising finding because the children were cooled to a temperature of  $28^\circ\text{C}$  during this interval. The lack of change in clearance may be a reflection of the low hepatic clearance of alfentanil, so that it is not dependent on flow. The short duration of CPB might have hindered the ability to identify changes in clearance during bypass. Sensitivity analysis suggested that clearance during CPB could decrease by as much as 50% without being detected by the regression. The model showed an increase in the size and intercompartmental clearance of the

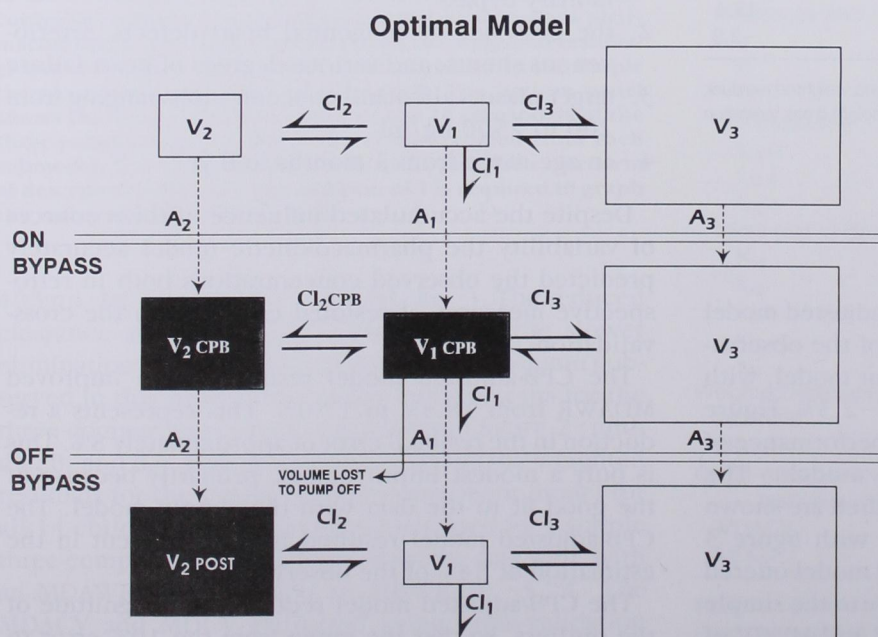


Fig. 4. Optimal cardiopulmonary-bypass-adjusted pharmacokinetic model. A change in four parameters,  $V_1$  on CPB,  $V_2$  on CPB,  $Cl_2$  on CPB, and  $V_2$  post-CPB statistically improved the model description of the data.

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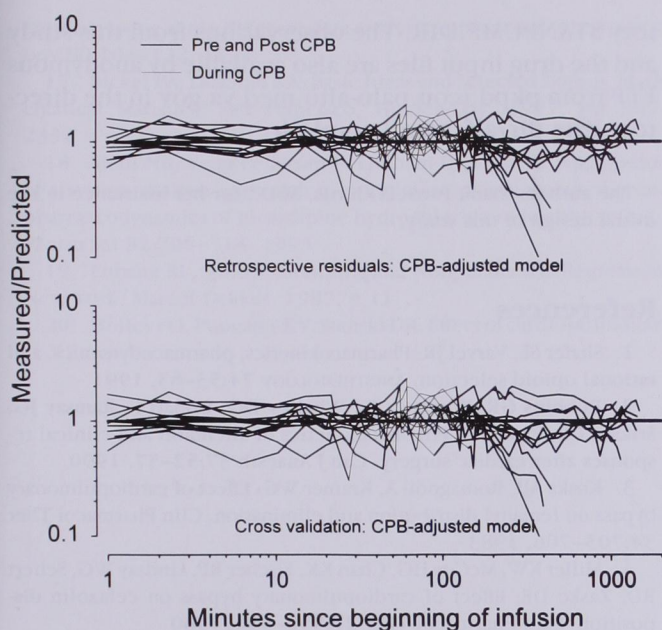


Fig. 5. The top panel shows the weighted residual errors over time for the weight-proportional, cardiopulmonary-bypass-adjusted three-compartment model. The bottom panel shows the cross-validation errors of the 14 submodels of the cardiopulmonary-bypass-adjusted three-compartment model in the child excluded from each submodel.

rapidly equilibrating peripheral compartment during bypass. It may be that this change in  $V_2$  reflects an increase in the free fraction of alfentanil, and associated increased partitioning in the tissues, caused by the lower temperature. We were not surprised that there was no change in the size or intercompartmental clearance of the slowly equilibrating compartment, because the first two time intervals (pre- and during CPB) were generally less than 1 hr. During this limited interval, very little information is provided about  $V_3$ , so its estimation in the model is almost entirely derived from the post-CPB samples. We again emphasize that such speculations are not relevant to the central point of the modeling exercise, which was to accurately describe the relationship between drug input and plasma drug concentration throughout the perioperative period in children undergoing CPB.

The modeling was performed using a pooled data technique. Such a technique may produce biased estimates of the pharmacokinetic parameters when the times, or presence, of the plasma samples are dependent on the pharmacokinetic parameters of the individual patient. That was not the case in this study. There were no samples less than the limits of detection of the

assay and the samples were all taken at times specified by the protocol independently of the clinical status of the patient. We used the pooled data approach previously to characterize the pharmacokinetics of drugs administered by CCIP.<sup>11,15,16,22</sup> In each of these cases, we prospectively tested the results, and found excellent performance of the parameters derived with this modeling technique. Thus, we have no reason to suspect that the pharmacokinetic parameters of either the simple or CPB-adjusted model would not yield good results when prospectively applied to a subsequent population.

Cross-validation provides a measure of the predictive ability of the model. While the residual error is a favorably biased estimate of the predictive ability of the model, cross-validation provides a nearly unbiased estimate of the predictive ability. The predictive accuracy of the simple three-compartment model decreased from 18.4% median absolute error as estimated by the weighted residuals to 18.9% median absolute error as measured using cross-validation. The predictive accuracy of the CPB-adjusted model decreased from 17.0% median absolute error using the weighted residuals to 18.4% median absolute error based on cross-validation. This suggests that the estimated models are likely to perform well in truly prospective trials.

Cross-validation is not a prospective trial, but it provides an estimate of the expected performance of the model in a truly prospective trial. A truly prospective trial provides an unbiased measure of the expected performance of the model, but only under identical experimental conditions. As observed in the methods, cross-validation provides a conservative measure of the expected performance of the model under identical experimental circumstances. This differs from a truly prospective test in two ways: (1) as mentioned in methods, the submodels tested are each constructed from less data than the final model, and thus would be expected to perform slightly less well than the final model; and 2) when the cross-validated model is tested prospectively, the experimental circumstances are not identical to the original study because the pharmacokinetics in the CCIP would be the newly estimated pharmacokinetics, not the pharmacokinetics used in the original study. The performance might be worse (or better) than estimated by the cross-validation analysis. If the pharmacokinetics are linear with respect to dose then the predictive accuracy of any pharmacokinetic parameter set should not be influenced by the dose administered. However, if the pharmacokinetics

are not linear with respect to dose, then a truly prospective trial might result in significantly worse performance than estimated using cross-validation. In the current study, the pharmacokinetics of alfentanil appear to be linear with dose. This can be inferred from figures 3 and 5, where the errors appear to be a constant fraction of the concentration, despite the concentrations spanning four orders of magnitude. Thus, the cross-validation provides a measure of the expected performance of the pharmacokinetics in a prospective study assuming identical experimental conditions other than the pharmacokinetics programmed into the CCIP.

Cross-validation provides an efficient method to use all of the available data for model development and testing. Validation of models often involves splitting studies into "learning" and "test" data sets. The model is developed in the learning set, and then tested "prospectively" by examining the accuracy of prediction of the test data. When data are very expensive or scarce, (e.g., pharmacokinetic studies in pediatric subpopulations), dividing the available data into learning and test sets reduces the accuracy of the final model by developing it from a subset of the full data. It also makes the performance estimated from the test data set less accurate, again because the estimate is based on a subset of the full data. Cross-validation, as performed here, provides an efficient method to use all data for both model development and validation, with the limitations discussed earlier. Cross-validation has been applied to a few prior pharmacokinetic analyses.<sup>18</sup>

In conclusion, we prospectively tested alfentanil pharmacokinetics in a population of children undergoing CPB, and developed new models to describe the pharmacokinetics of alfentanil in this population. The new model included allowing for changes in the volumes and clearances at the onset and conclusion of CPB. The final model described the 478 observations with a median error of 17.0%. Cross-validation suggested the model may perform nearly as well in prospective studies. The parameters of the final model may improve our ability to provide anesthesia and postoperative analgesia in children undergoing open heart surgery. Additionally, the approach to modeling pharmacokinetics in the presence of the acute changes of CPB may improve our ability to accurately characterize pharmacokinetics of many drugs in patients undergoing CPB.

### Addendum

The STANPUMP program is available by anonymous FTP from [pkpd.icon.palo-alto.med.va.gov](ftp://pkpd.icon.palo-alto.med.va.gov) in the direc-

tory STANPUMP.DIR. The observations from this study and the drug input files are also available by anonymous FTP from [pkpd.icon.palo-alto.med.va.gov](ftp://pkpd.icon.palo-alto.med.va.gov) in the directory data.dir/alfentanil.ccipl.dir.

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