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Effects of Cardiopulmonary Bypass on Sufentanil Pharmacokinetics in Patients Undergoing Coronary Artery Bypass Surgery

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Background: **Complete pharmacokinetic modeling, including assessment of the effect of cardiopulmonary bypass (CPB) on sufentanil disposition, has not been reported. The aims of this investigation were to define a model that accurately predicted sufentanil concentrations during and after cardiac surgery and to determine if CPB had a clinically significant impact on sufentanil pharmacokinetics.**

Methods: **Population pharmacokinetic modeling was applied to data from 21 patients undergoing coronary artery bypass grafting. The predictive ability of models was assessed by calculating bias, accuracy, and measured:predicted concentration ratios *versus* time. A simple three-compartment model, without covariates, was initially compared with models having weight or gender as covariates and was subsequently used as the foundation for multiple CPB-adjusted models (allowing step-changes of parameters at the start or end of CPB). The primary criterion for choosing more complex models was a significant improvement in log-likelihood; secondary criteria were significant improvement in bias or accuracy.**

Results: **Neither covariate (weight or gender) models improved bias or accuracy compared with the simple three-compartment model. A final CPB-adjusted model with V2 and Cl3 changing at the start of CPB and V1, Cl2, and Cl3 changing at the end of CPB had significantly greater log-likelihood values when compared with the simple three-compartment model and with less elaborate CPB-adjusted models. However, bias and accuracy for this final model were not significantly different from the simple three-compartment model.**

Conclusions: **When sufentanil is infused at a constant rate, with initiation of CPB, a pharmacokinetic model adjusted for CPB predicts that the sufentanil concentration will decrease ~17% and that it will begin to return to the prebypass concentration 12 min after initiation of CPB. At the end of CPB, this model also predicts a brief spike of the sufentanil concentration. These predictions reflect changes in the measured sufentanil concentrations. However, compared with a simple, three-compartment model, incorporating step-changes of pharmacokinetic parameters at the start or end of cardiopulmonary bypass (or both) did not significantly improve overall perioperative prediction of measured sufentanil concentrations. This suggests that CPB has clinically insignificant effects on sufentanil kinetics in adults.**

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ALTHOUGH sufentanil has been used extensively in cardiac anesthesia since the mid-1980s, the effect of cardiopulmonary bypass (CPB) on sufentanil pharmacokinetics has not been defined. Physiologic changes associated with CPB, such as abnormal blood flow, hemodilution, hypothermia, and the systemic inflammatory response, could potentially alter drug disposition.[1]

Rapid recovery of ventilatory drive and early tracheal extubation have become priorities in cardiac anesthesia. Earlier tracheal extubation is associated with improved resource utilization[2] without increasing morbidity.[3] Maximizing the benefits of opioids while also minimizing the duration of postoperative respiratory depression mandates precise administration. An accurate pharmacokinetic model is a prerequisite for designing dose regimens that reliably achieve these goals.

Our objectives were to define a pharmacokinetic model that accurately predicts sufentanil concentrations before, during, and after CPB in patients undergoing coronary artery bypass grafting and to determine if CPB had clinically important effects on sufentanil pharmacokinetics. Accordingly, we assessed multiple models that allowed for step-changes in pharmacokinetic parameters at the initiation or termination of CPB (or both). Other investigators have used a similar approach to investigate the pharmacokinetics of alfentanil in children[4] and propofol in adults[5] undergoing surgery using CPB. We determined a final pharmacokinetic model using log-likelihood for model discrimination, and we compared the predictive ability of this CPB-adjusted model with a simple three-compartment model that did not permit changes in parameters at the start or end of CPB.

Materials and Methods

These studies were approved by the University of Manitoba Biomedical Research Ethics Board, and informed consent was obtained from all participants. Predefined exclusion criteria included the following: age > 80 yr, weight > 110 kg, baseline preoperative mean arterial pressure > 100 mmHg, previous cardiac surgery, left ventricular ejection fraction < 0.3 or reported "severe" left ventricular dysfunction, unstable angina requiring intravenous nitroglycerin or continuous electrocardiographic monitoring, or previous adverse reaction to any of the study drugs.

Clinical Protocol

On the morning of surgery, all patients received ranitidine 150 mg *per os*, lorazepam 40 μg/kg *per os*, and their usual medications. Sufentanil was administered with a target-controlled infusion (TCI) system. The components of the TCI system were an infusion pump interfaced with a computer controlled by the program STANPUMP.‡ Parameters from previous studies of sufentanil pharmacokinetics before CPB[6] and the rate constant for blood-effect site equilibration (k_{e0})[7] were entered into STANPUMP. The TCI was initially set to deliver a sufentanil loading dose of 0.5 μg/kg. Two minutes after starting the sufentanil infusion, thiopental 3–5 mg/kg was administered intravenously over 30 s. Initial neuromuscular blockade was achieved with succinylcholine, the trachea was intubated, and muscle relaxation was maintained with vecuronium. At least 5 min before skin incision, a minimum end-tidal concentration of isoflurane of 0.25% was maintained. After skin incision, but before CPB, the end-tidal isoflurane concentration was titrated to maintain heart rate and mean arterial pressure within 20% of preoperative values. During CPB, isoflurane was administered *via* the oxygenator to maintain mean arterial pressure between 50 and 90 mmHg. After separation from bypass isoflurane was titrated at the discretion of the attending anesthesiologist.

At least 5 min before skin incision STANPUMP was reset to maintain a target effect site sufentanil concentration of 0.7 ng/ml. Five minutes after sternotomy, the target concentration was decreased to 0.5 ng/ml. Thirty minutes after initiation of CPB, the target concentration was reduced further to 0.15 ng/ml. The sufentanil TCI was stopped at the end of surgery. No other intravenous anesthetics or adjuvants were administered before or during CPB. Low-dose propofol infusions (1–4 $mg \cdot kg^{-1} \cdot h^{-1}$) were begun after sternal closure.

The CPB circuit was primed with 700 ml of lactated Ringer's solution and 500 ml of pentastarch 10%. CPB was conducted using mild hypothermia (core temperature >33°C), α-stat pH management, pulsatile flow during the period of aortic cross-clamping, and nonsilicon hollow-fiber membrane oxygenators. All patients were rewarmed to a rectal temperature of ≥36°C before separation from CPB.

Serum sufentanil concentrations were measured in arterial blood sampled at these nominal times:

- 3, 5, 15, and 30 min after the start of the sufentanil TCI,
- then every 30 min until, and also just before, initiation of CPB,
- 5, 15, 30, 40, and 60 min after initiation of CPB, and subsequently every 30 min until separation from CPB,
- just after separation from CPB and at the end of surgery, and
- postoperatively, every 2 h until 12 h, and then every 4 h until 24 h from the start of the sufentanil TCI.

Sufentanil concentrations were measured by radioimmunoassay in the Bioanalytical Department of the Janssen Research Foundation, Beerse, Belgium. The limit of quantification was 0.01 ng/ml. The measured sufentanil concentrations just before initiation of CPB and 5 and 30 min after initiation of CPB were compared by repeated-measures analysis of variance. The sufentanil concentrations measured in the last sample drawn during CPB, the postCPB sample, and at the end of surgery were also compared using repeated-measures analysis of variance. The Tukey test was used for pairwise comparisons if analysis of variance returned $P < 0.05$.

Determination of the Base Model

Population pharmacokinetic modeling (naïve-pooled data technique) was done with NONMEM V (Globomax LLC, Hanover, MD). A total of 438 samples from the 21 patients were available for modeling. Compartmental volumes (V1, V2, and V3) and clearances (Cl1: from compartment 1, or elimination clearance; Cl2: into and out of compartment 2, or rapid intercompartmental clearance; and Cl3: into and out of compartment 3, or slow intercompartmental clearance) were estimated directly by NONMEM. Initially, parameters for a simple three-compartment model with no covariates were estimated. We then estimated parameters for models with either weight (all six parameters scaled to weight) or gender (all six parameters unique for each gender) as covariates. We compared these three models to select the base model for development of the CPB-adjusted pharmacokinetic models. The primary criterion for acceptance of more complex models was an increase in log-likelihood of at least 2 for each additional parameter.[4,5,8] Differences in log-likelihood were calculated by dividing the difference in the NONMEM objective function by 2. Secondary criteria were significant ($P < 0.05$) improvement in either the prediction error (PE), or the absolute prediction error (APE).§ The median values of PE and APE were calculated for each subject and each model and then compared with either the rank sum test or the Kruskal-Wallis test, as appropriate.

Development of CPB-Adjusted Models: First Iteration

We then estimated parameters for 18 alternative models adjusted for CPB by allowing parameters to change when CPB was initiated or terminated. Each of the six

‡ STANPUMP is available from its author, Steven L. Shafer, M.D., Department of Anesthesia, Stanford University, via the World Wide Web at http://anesthesia.stanford.edu/pkpd/. Accessed March 29, 2004.

§ PE = $([Sufentanil]_{measured} - [Sufentanil]_{predicted}) / [Sufentanil]_{predicted} \times 100\%$. APE is its absolute value.

parameters of the base model (V1, V2, V3, Cl1, Cl2, and Cl3) was allowed to change in the following manner:

- at initiation of CPB (but remaining unchanged thereafter), or
- at separation from CPB, or
- to have a unique value during CPB (changing at initiation of CPB, but reverting to the pre-CPB value at separation from CPB).

Log-likelihood values for these models were assessed to identify the model to be used as the foundation for development of more complex CPB-adjusted models.

Development of CPB-Adjusted Models: Second Iteration

The model that allowed V2 to change at the start of CPB was used as the foundation for more elaborate CPB-adjusted models. Models that allowed more than one parameter to change at the start of CPB were then developed and compared using the log-likelihood criterion. On this basis, the model that allowed both V2 and Cl3 to change at the start of CPB was used as the foundation for the third iteration.

Development of CPB-Adjusted Models: Final Iteration

Starting with the model that allowed both V2 and Cl3 to change at the start of CPB, we then assessed more complex models that allowed each of the six parameters to change at the end of CPB. On the basis of the log-likelihoods of these models, we then developed models that allowed more than one parameter to change at the end of CPB, in addition to the changes of V2 and Cl3 at the start of CPB. The final CPB adjusted model was identified when adding another parameter change at the end of CPB failed to increase log-likelihood by greater than 2.

This predictive ability of this final CPB-adjusted model was compared with the simple, three-compartment model without covariates (weight, gender) and without adjustments for CPB. Median values for PE and APE for each subject and model were compared using the rank-sum test. The simple three-compartment model and the final CPB-adjusted model were also assessed by graphic analysis of the measure:predicted concentration ratios *versus* time. For all statistical analyses, null hypotheses were rejected when P was less than 0.05.

Comparison of Models Using Simulation

Sufentanil concentration *versus* time curves were predicted by applying both the simple three-compartment model and the final CPB-adjusted model to a dose regimen designed to achieve two goals: near maximal opioid effects before CPB and sufentanil concentrations compatible with adequate spontaneous ventilation at the end of surgery or shortly thereafter. This simulated dose regimen can be implemented with infusion pumps that are currently widely available to anesthesiologists (no TCI system required). The conditions for these simulations were:

- a loading dose of 40 μg, followed by
- an infusion of sufentanil at 66 μg/h until CPB is begun 80 min after administration of the loading dose, then infusing sufentanil at 12 μg/h until the end of surgery at 240 min.
- CPB is terminated at 200 min after administration of the loading dose (duration 120 min).

Table 1. Demographics (n = 21)

Age (yr)	67.0 ± 9.1
Weight (kg)	82.5 ± 13.5
Male/Female	14/7
Chronic medications	
β-adrenoceptor antagonists	17 (81%)
Calcium-channel blockers	3 (30%)
Angiotension-converting enzyme inhibitors	4 (18%)
Long-acting nitrates	14 (75%)
Sufentanil doses administered	
Total (μg)	144 ± 33
Weight-normalized (μg/kg)	1.7 ± 0.3
Elapsed times	
Induction of anesthesia—end surgery (h)	4.4 (2.7–8.0)
Start of CPB—separation from CPB (h)	2.0 (0.9–3.6)

Data are presented as mean ± SD, number of patients (percent), or median (range).

CPB = cardiopulmonary bypass.

Results

Demographic data are shown in table 1. The measured sufentanil concentrations just before initiation of CPB and 5 and 30 min after initiation of CPB are shown in the left panel of figure 1. The mean concentrations at these three times were 0.47, 0.35, and 0.40 ng/ml, respectively. The pre-CPB concentrations were significantly different ($P < 0.02$) from the concentrations 5 and 30 min after initiation of CPB. The right panel of figure 1 displays the last sufentanil concentrations measured during CPB, the concentrations immediately after separation from CPB, and at the end of surgery. The mean concentrations at these times were 0.15, 0.22, and 0.15 ng/ml, respectively. Pairwise analysis indicated that the concentrations just after separation from CPB were significantly different ($P < 0.001$) from the other two times.

Determination of the Base Model

The simple, three-compartment model without any covariates had an overall median (interquartile range) PE of −1.7% (−18.6%, +20.5%), and the overall median APE was 19.4% (9.1%, 35.5%). Adding weight or gender as a covariate increased log-likelihood by 1.7 and 2.3, respectively (table 2). The overall median values for PE and APE for the simple three-compartment model and

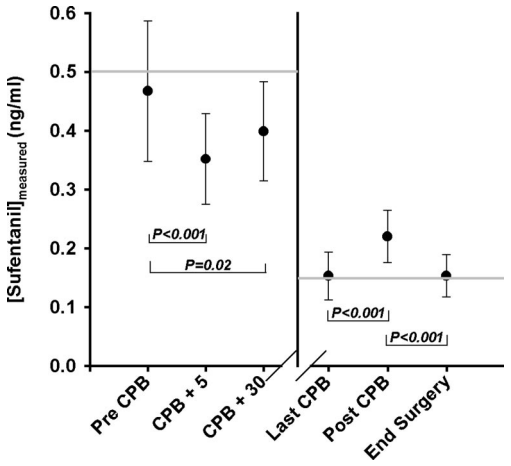

Fig. 1. Mean ± SD measured sufentanil concentrations before and after the start of cardiopulmonary bypass (CPB) and before and after termination of CPB. The gray horizontal lines represent the target sufentanil concentrations for each period. *Pre CPB* = just before CPB; *CPB + 5* = 5 min after the start of CPB; *CPB + 30* = 30 min after the start of CPB; *Last CPB* = last sample drawn during CPB; *Post CPB* = just after separation from CPB; *End Surgery* = end of surgery.

the two covariate (gender and weight) models are shown in table 2. When the median values of PE and APE from each subject were compared, there were no significant differences between these three models ($P = 1.0$ for both PE and APE). Thus, compared to the simple, three-compartment model, neither covariate improved predictive ability. Given the barely significant change in log-likelihood using gender as a covariate and the absence of any improvement in predictive ability, we chose the simple, three-compartment model as the base model for developing CPB-adjusted models. The parameters of this model are as follows: V1, 19.4 l; V2, 28.4 l; V3, 277 l; Cl1, 0.90 l/min; Cl2, 2.26 l/min; and Cl3, 0.86 l/min.

Development of CPB-adjusted Models: First Iteration

The results of this iteration are shown in table 3. Compared to the base model, all six models that allowed one parameter to change at the start of CPB (remaining constant thereafter) increased log-likelihood by >2 (range, 4.45–41.03). Similarly, each of the six models that allowed one parameter to have unique value during CPB increased log-likelihood by >2 (range, 2.56–29.13). Of the six models that allowed a step-change in a parameter at separation from CPB, only two models increased log-likelihood by >2: the models that allowed V1 or V2 to change, with increases in log-likelihood of 6.03 and 7.36, respectively. The overall median PE for these 18 models ranged from −1.89% to +0.59%, compared with −1.70% for the base model (table 3). The overall median APE for the CPB-adjusted models ranged from 16.25% to 19.89%, compared with 19.39% for the base model (table 3).

Fourteen of the 18 CPB adjusted models met the log-likelihood criterion (table 3). Of these, the model in which V2 changed at the start of CPB had the greatest increase in log-likelihood compared to the simple, three-compartment model. Therefore, this model was used as the basis for the next iteration.

Table 2. Comparison of Covariate Models

Covariate	PE (%)	APE (%)	Change in Log-Likelihood*
None	−1.7 (−18.6, +20.5)	19.4 (9.1, 35.5)	–
Gender	−2.0 (−19.3, +23.0)	20.6 (9.8, 33.3)	2.31
Weight	+0.01 (−19.7, +21.2)	20.4 (9.8, 34.5)	1.76

Values are median (interquartile range).

APE = absolute prediction error; PE = prediction error.

* Per additional parameter, compared to the model without covariates.

Table 3. Comparison of Simple and CPB-Adjusted Models: First Iteration

	Median PE	Median APE	Increase in Log-Likelihood*
Simple, 3-compartment model, not adjusted for CPB	−1.7%	19.4	–
Parameter changes at start CPB, no change at end CPB:			
Cl1	−0.9%	18.3%	4.79
Cl2	−1.1%	18.8%	15.72
Cl3	−1.3%	19.6%	16.14
V1	−0.2%	18.6%	4.45
V2	−0.7%	18.3%	41.03
V3	−0.5%	18.1%	6.99
Parameter changes at start CPB, reverts to pre-CPB value at end CPB:			
Cl1	−0.6%	19.9%	9.25
Cl2	−1.4%	18.2%	22.12
Cl3	+0.2%	19.5%	19.39
V1	−0.4%	18.6%	11.76
V2	+0.6%	16.3%	29.13
V3	−1.2%	19.8%	2.56
Parameter changes at end CPB:			
Cl1	−1.9%	19.7%	0.34
Cl2	−1.7%	19.3%	0.00
Cl3	−1.7%	19.4%	0.01
V1	−1.5%	19.6%	6.03
V2	−0.3%	19.4%	7.36
V3	−1.5%	19.9%	1.79

APE = absolute prediction error; Cl1 = elimination clearance; Cl2 = rapid intercompartmental clearance; Cl3 = slow intercompartmental clearance; CPB = cardiopulmonary bypass; PE = prediction error; V1, V2, V3 = pharmacokinetic compartment volumes.

* Compared with the simple, 3-compartment model. An increase in log-likelihood of >2 is statistically significant.

Development of CPB-adjusted Models: Second Iteration

In this iteration, models that allowed V2 plus a second parameter to change at the start of CPB were assessed sequentially, according to the effect of second parameter on log-likelihood in the previous iteration. Allowing both

Table 4. Comparison of CPB-Adjusted Models (Final Iteration)

V2 and Cl3 Change at Start CPB, plus Parameter Changes at End CPB	Increase in Log-Likelihood*	
	Value	Compared to Model
V1	3.34	V2 and Cl3 change at start CPB
V2	0.88	
V3	3.69	
Cl1	0.04	
Cl2	5.10	
Cl3	3.44	
V1 & Cl2	2.58	V2 and Cl3 change at start CPB, Cl2 changes at end CPB
V3 & Cl2	2.47	
Cl2 & Cl3	3.23	
V3, Cl2, & Cl3	1.00	V2 and Cl3 change at start CPB, Cl2 and Cl3 change at end CPB
Final CPB-Adjusted Model:		
V1, Cl2, & Cl3	3.02	
V1, V3, Cl2, & Cl3	0.57	V2 and Cl3 change at start CPB, V1, Cl2 and Cl3 change at end CPB

Cl1 = elimination clearance; Cl2 = rapid intercompartmental clearance; Cl3 = slow intercompartmental clearance; CPB = cardiopulmonary bypass; V1, V2, V3 = pharmacokinetic compartment volumes.

* Per additional parameter.

V2 and Cl3 to change at the start of CPB increased log-likelihood by 3.78 compared with the model in which only V2 changed. The model that allowed Cl2 to change in addition to V2 did not increase log-likelihood by more than 2. Consequently, we then assessed the model that allowed V2 and Cl3 plus Cl2 to change at the start of CPB; this model increased log-likelihood by only 1.54 when compared to the allowing V2 and Cl3 to change. Therefore, we used the model that allowed V2 and Cl3 to change at the start of CPB as the foundation for the final iterations.

Development of CPB-adjusted Models: Final Iterations

In the first stage of these iterations, we estimated six models, each allowing one of the six model parameters to change at the end of CPB in addition to having V2 and Cl3 change at the start of CPB. Allowing V2 or Cl1 to change at the end of CPB did not produce a significant increase in log-likelihood (table 4, top group). In this group, changing Cl2 at the end of CPB produced the greatest increment in log-likelihood (table 4, top group). Accordingly, we used this model as the foundation for the next stage.

In the next stage, we estimated models that allowed V2 and Cl3 to change at the start of CPB, and Cl2 plus one other parameter (V1, V3, or Cl3) to change at the end of CPB. All three of these models increase log-likelihood by more than 2, but the increases were relatively small and not significantly different from each other (table 4, second group). Allowing Cl2 and Cl3 to change at the end of CPB produced the greatest increase in log-likelihood (table 4, second group).

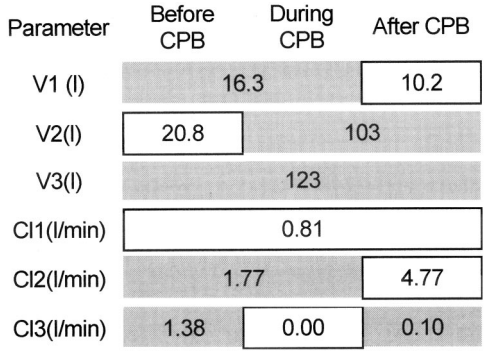

Fig. 2. The final cardiopulmonary bypass (CPB)-adjusted model. At the start of CPB, both V2 and Cl3 change. At the end of CPB, V1, Cl2, and Cl3 change. *CPB* = cardiopulmonary bypass; *V1, V2*, and *V3* = pharmacokinetic compartment volumes; *Cl1* = elimination clearance; *Cl2* = rapid intercompartmental clearance; *Cl3* = slow intercompartmental clearance.

Therefore, in the final stage we used the model that allowed V2 and Cl3 to change at the start of CPB and Cl2 and C3 to change at the end of CPB as the base model. We tested all remaining possible combinations of the parameters that increased log-likelihood significantly in the first stage of this iteration, allowing the following to change at the end of CPB:

- V1, Cl2, and Cl3; or
- V3, Cl2, and Cl3; or
- V1, V3, Cl2, and Cl3

Compared with the base model for this iteration, only the model that allowed V1, Cl2, and Cl3 to change at the end of CPB significantly increased log-likelihood (table 4, third group). Allowing four parameters (V1, V3, Cl2, and Cl3) did not significantly improve log-likelihood (table 4, bottom group). Therefore, our final CPB-adjusted model was the one in which V2 and Cl3 changed at the start of CPB and V1, Cl2, and Cl3 changed at the end of CPB. This model is depicted in figure 2.

Comparison of Predictive Ability

The log-likelihoods and the overall PE and APE of the simple three-compartmental model (with no covariates or adjustments for CPB) and the final CPB-adjusted model are shown in table 5. The change in log-likelihood for the CPB-adjusted model compared with the simple three-compartment model was 56.16, or 11.23 for each additional parameter—an increase in log-likelihood of 2 for each additional parameter is statistically significant. When the predictive ability of the final CPB-adjusted model and the base model were compared, there were no significant differences: rank-sum testing of the median values of PE and APE returned *P* values of 0.89 and 0.37, respectively. The measured:predicted concentration ratios *versus* time for both models are shown in figures 3 and 4. No time-related changes in bias are evident.

Table 5. Comparison of Predictive Ability: Simple *versus* Final CPB-Adjusted Models

	PE (%)	APE (%)	Log-Likelihood	Change in Log-Likelihood*
Simple 3-compartment model	−1.7 (−18.6, +20.5)	19.4 (9.1, 35.5)	281.38	–
Final CPB-adjusted model	−0.1 (−16.3, +16.6)	16.6 (8.3, 30.0)	337.54	11.23

APE = absolute prediction error; CPB = cardiopulmonary bypass; PE = prediction error.

* Per additional parameter, compared with the simple 3-compartment model.

Comparison of Models Using Simulation

The plasma concentration *versus* time curves predicted by the simple three-compartment model and the final CPB-adjusted model, for the same dose regimen, are shown in figure 5. After administration of a loading dose of 40 μg^{-1}, followed by an infusion of 66 $\mu g/h$, both models predict a rapid decrease in concentration to just less than 0.7 ng/ml within 10 min. As the infused sufentanil accumulates, after approximately 20 min, both models predict a slowly increasing concentration that remains close to 0.7 ng/ml. At the start of CPB, the infusion rate is decreased to 12 $\mu g/h$, and, although both models predict a rapid decrease of the concentrations, the CPB-adjusted model predicts a longer lasting rapid decrease. This part of the simulation indicates that the effect of reducing the infusion rate at the start of CPB has a greater impact on sufentanil concentrations than the effect of CPB on sufentanil kinetics. Another simulation, in which the infusion rate was not decreased at the start of CPB, was also done. Under these conditions, the CPB-adjusted model predicts a decrease to ~0.6 ng/ml. However, this decrease is short-lived, and the predicted concentration begins to increase 12 min after initiation of CPB.

At the end of CPB, the concentration predicted by the CPB-adjusted model is 0.23 ng/ml, compared to 0.22 ng/ml as predicted by the simple model.

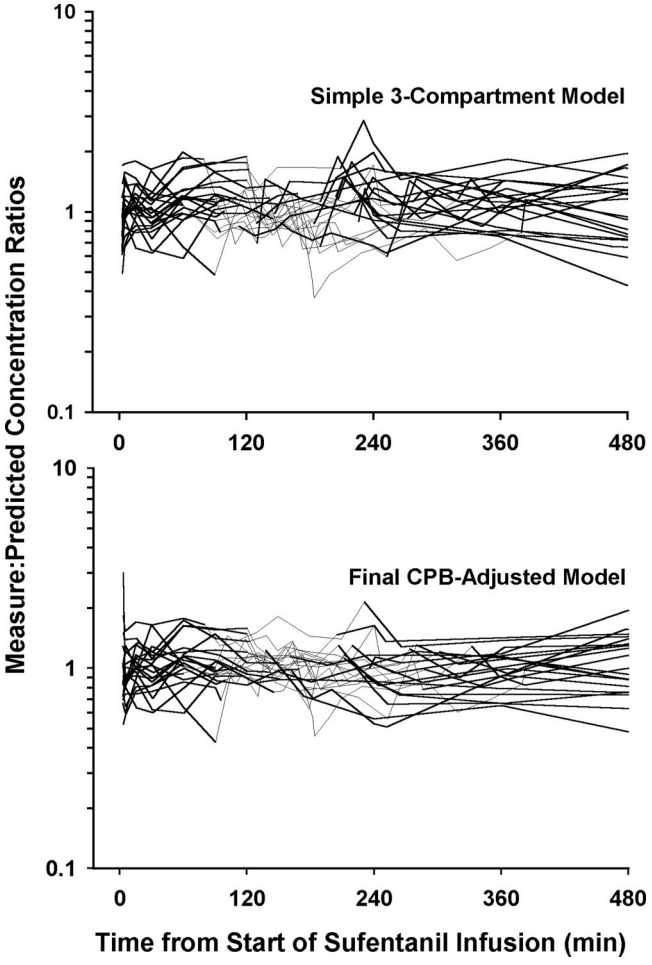

Fig. 3. The measured:predicted concentration ratios *versus* time for the first 8 h after the start of the sufentanil target-controlled infusion. The upper graph shows the ratios for the simple, three-compartment model; the lower graph depicts the ratios for the final, cardiopulmonary bypass (CPB)-adjusted model. Each plot represents data from one subject, and the finer segment of each plot indicates the time from the last sample before CPB to the last sample during CPB.

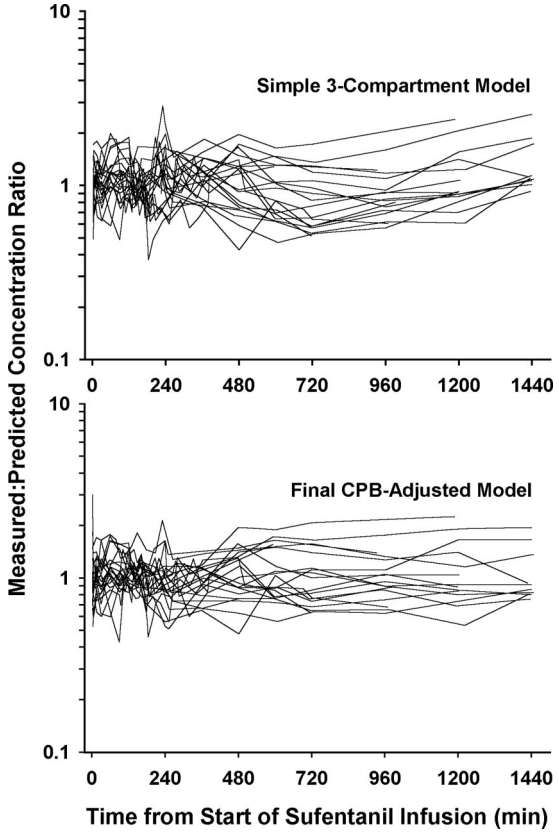

Fig. 4. The measured:predicted concentration ratios *versus* time for the entire study duration for the simple model and the cardiopulmonary bypass (CPB)-adjusted model. Each plot represents data from one subject.

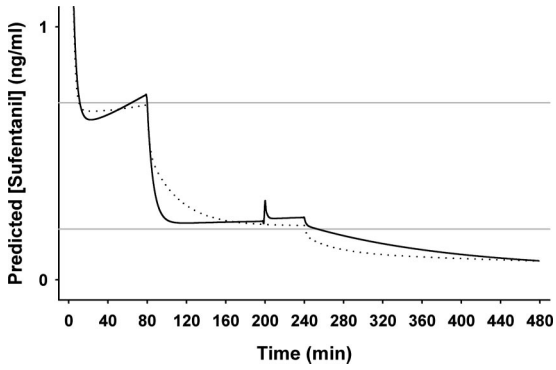

Fig. 5. Simulated plasma sufentanil concentration *versus* time curves predicted by the simple three-compartment model (*dotted line*) and the final cardiopulmonary bypass (CPB)-adjusted model (*solid line*) for a specific sufentanil dose regimen. The loading dose is 40 μg, followed by a constant infusion of 66 μg/h, until CPB is initiated at 80 min after administration of the loading dose. At 80 min, the infusion rate is decreased to 12 μg/h and maintained at this rate until the end of surgery. CPB is terminated at 200 min.

After termination of CPB, the adjusted model predicts a brief spike of the concentration, followed by a plateau that remains ~0.03 ng/ml higher than the concentration predicted by the simple model until the end of surgery at 240 min, a difference of less than 15%. When the infusion is stopped at the end of surgery, the simple model initially predicts a more rapid decline in the sufentanil concentration: 27% during the next 10 min, compared with only 17% for the CPB-adjusted model. Subsequently, the concentrations predicted by the models converge, and by 480 min they are the same.

Discussion

During the past 25 yr potent opioids have had an important role in cardiac anesthesia. Despite this common and longstanding practice, no model has been published that has assessed the impact of CPB on sufentanil pharmacokinetics and that accurately predicts sufentanil concentrations during surgery using CPB. Our CPB-adjusted model provides cardiac anesthesiologists with fundamental information required for predicting the sufentanil concentration *versus* time curve that any specified dose regimen will produce. During the latter part of the 1990s, rapid recovery of respiratory drive and early tracheal extubation became priorities in cardiac anesthesia because of improved resource utilization without any adverse effects on morbidity.[2,3] In combination with pharmacodynamic information, which relates drug concentrations to drug effects,[9,10] our model provides a scientific basis for designing sufentanil dose regimens for patients undergoing cardiac surgery that can maximize the benefits of opioids perioperatively, such as suppression of responses to noxious stimuli and effective postoperative analgesia, while minimizing the risk of prolonged postoperative respiratory depression.

Measured Sufentanil Concentrations

The sufentanil concentrations measured 5 min after the start of CPB were significantly lower that the concentrations just before CPB. This is expected because of hemodilution resulting from mixing of the CPB circuit priming solution and blood. The decrease in mean sufentanil concentrations from 0.47 to 0.35 ng/ml is a 26% change in concentration. Thirty minutes after initiation of CPB, the mean sufentanil concentration had increased to 0.40 ng/ml, which was still significantly different from the pre-CPB concentration. During this 30-min period, the target sufentanil concentration remained at the pre-CPB setting of 0.5 ng/ml. Thirty minutes after the start of CPB, the target concentration was reduced to 0.15 ng/ml. This interrupts the TCI until STANPUMP predicts that the effect site concentration is approaching 0.15 ng/ml. The duration of this interruption largely depends on the total dose of sufentanil administered before reducing the target concentration.

Ideally, we would have kept the target concentration at the pre-CPB setting for longer than 30 min after initiation of CPB to determine if the measured concentrations would return to pre-CPB concentrations. However, simulation of such TCI regimens indicated that they would produce sufentanil concentrations that would not be compatible with adequate spontaneous ventilation at the end of surgery. Unnecessary prolongation of postoperative sufentanil-induced respiratory depression in study patients was not acceptable, given our clinical resources.

Sufentanil concentrations measured just after separation from CPB were significantly greater than the last concentrations measured during CPB, 0.22 *versus* 0.15 ng/ml. This represents a 47% increase in concentration. This is likely a result of elution of sufentanil from the lungs with restoration of pulmonary blood flow during separation from CPB, as has been observed with fentanyl.[11] Just before initiation of CPB, the lungs were exposed to relatively high concentrations of sufentanil, averaging 0.47 ng/ml. The lungs have considerable affinity for fentanyl and other lipophilic organic bases,[12] including sufentanil.[13] Improved perfusion of peripheral vascular beds with restoration of more physiologic blood flow after separation from CPB could also contribute to elution of sufentanil from tissues into the blood. However, as others have observed this is a very transient phenomenon for both fentanyl[11] and sufentanil.[14] At the end of surgery, the mean sufentanil concentration had returned to 0.15 ng/ml, equal to the last concentration measured during CPB. This mean measured concentration at the end of surgery was also identical to the target concentration setting.

We measured total sufentanil concentrations and did not investigate changes in binding of sufentanil to plasma proteins. Hemodilution at initiation of CPB will dilute free drug, protein-bound drug, and binding pro-

teins equally; under these circumstances, the law of mass action dictates that the free fraction of drug must increase. This offsets the reduction in free drug concentration to some extent. The phenomenon has been documented for alfentanil: a 55% decrease in total alfentanil concentrations with initiation of CPB was associated with only a 13% decrease in free drug concentrations.[15] Therefore, the 26% decrease in total concentration we observed at initiation of CPB would have been accompanied by a lesser decrease in free sufentanil concentrations.

Model Development and Assessment

Accurate and precise pharmacokinetic models are prerequisites for developing dose regimens to achieve and maintain desired target concentrations. To be clinically useful, a pharmacokinetic model must be free of bias (median PE near zero, without any time-related change in bias), and it must have adequate precision—a median APE of $< 30\%$ has been recommended.[16]

The first step in our modeling strategy was to determine the parameters for a simple three-compartment model. This initial model was the benchmark against which we compared more complex models that included various covariates or adjustments for CPB. An increase in log-likelihood of >2 (for each added parameter) has been used as the criterion for model discrimination—identifying the simplest model that accurately describes the observed data.[4,5,8] However, in the context of clinical utility, we believe that a pharmacokinetic model is better only if it significantly improves predictive ability by decreasing PE or APE. Accordingly, we also compared the PE and APE of the more complex models and the simple, three-compartment model.

Compared with the simple three-compartment model without covariates, adding gender as a covariate produced a small, but significant, increase in log-likelihood. Using weight as a covariate did not significantly increase log-likelihood. However, the gender-covariate model did not improve PE or APE (table 2). This is not surprising, because the initial model had minimal overall bias (median PE = −1.7%) and adequate precision (median APE = 19.4%), thus meeting suggested criteria for clinical utility.[16] This finding is consistent with our previous study of distribution-phase sufentanil pharmacokinetics in patients undergoing coronary artery bypass grafting, which showed that neither gender, weight, or concomitantly administered medications (lorazepam, morphine-scopolamine, clonidine, or propofol) significantly improved predictive ability.[6] Because adding gender as a covariate did not improve predictive ability, we used the three-compartment model without any covariates as the foundation for developing models that allowed step-changes in pharmacokinetic parameters at the start and end of CPB.

Using a sequential reiterative modeling strategy, we identified a final, CPB-adjusted pharmacokinetic model that significantly improved log-likelihood. This model had a total of 11 parameters, which are depicted in figure 2. This model increased log-likelihood by 11.23 for each of the additional five parameters, compared with the simple three-compartment model. However, when the median PE and APE of the CPB-adjusted model and the simple three-compartment model were compared, there were no significant differences.

In the final CPB-adjusted model, the near-zero estimate of Cl3 during CPB deserves comment (the actual NONMEM estimate was $1.97 \cdot 10^{-1}$ l/min). This means that virtually no sufentanil moves in or out of the third compartment during CPB; in essence, the third compartment drops out of the model during CPB. After separation from CPB, Cl3 remains very low, 0.10 l/min. Given the limitations of compartmental modeling, the *in vivo* changes in sufentanil disposition that cause this phenomenon cannot be identified. However, this observation indicates that the drug in the third compartment is essentially sequestered at the start of CPB.

How can we reconcile the paradox of significant changes in measured sufentanil concentrations at the start and end of CPB with the failure of the CPB-adjusted model to improve significantly predictive ability? After initiation of CPB, the decrease in the mean measured sufentanil concentration was relatively small, 26%. Although the mean concentration at 30 min after the start of CPB had increased to 85% of the pre-CPB concentration, it was still significantly lower at that time. The relative increase in concentration after separation from CPB was greater, 45%. However, this increase was very transient; the immediate postCPB concentration of 0.22 ng/ml decreased rapidly to 0.15 ng/ml by the end of surgery. Sufentanil is taken up extensively by tissues because it is highly lipophilic. Extensive tissue reservoirs will buffer any acute decrease in the blood concentration of sufentanil, such as occurred with initiation of CPB. The large tissue capacity for uptake of sufentanil will also buffer any acute increase in concentration; hence, the rapid decrease after the immediate postCPB increase. Thus, the "signal" produced by systemic changes in sufentanil concentration at the start and end of CPB is small compared to the background "noise" of random variability. We conclude that because of its high lipid solubility, the potential impact of CPB on sufentanil pharmacokinetics is rendered insignificant in comparison to other factors that cause pharmacokinetic variability.

Comparison of Models Using Simulation

To better understand the clinical implications of our results, we simulated the concentration *versus* time curves for a specific dose regimen that can be delivered without a TCI system. We have previously shown that sufentanil concentrations in the range of 0.7 ng/ml produce near-maximal opioid effects in patients undergoing

coronary artery bypass grafting, during the period before CPB.[9] At the end of surgery, concentrations <0.2 ng/ml should permit adequate spontaneous ventilation.[10] The simulations indicate that, with either model, a loading dose of 40 μg, followed by an infusion of 66 μg/h will maintain a predicted sufentanil plasma concentration close to 0.7 ng/ml during the pre-CPB period. If the infusion is decreased to 12 μg/h when CPB is initiated, the predicted concentrations decrease and are similar at the end of CPB (0.23 ng/ml for the CPB-adjusted model, 0.22 ng/ml for the simple model). At the end of surgery, the CPB adjusted model predicts a concentration of 0.25 ng/ml, compared with a concentration of 0.21 ng/ml for the simple model. Another simulation, in which the infusion rate was not decreased at the start of CPB, predicted that sufentanil concentrations would decrease by ~17%, and that 12 min after initiating CPB the concentration would begin to increase.

When the infusion is stopped at the end of surgery, the simple model predicts an initially more rapid decrease of the sufentanil concentrations. However, the concentration *versus* time curves soon begin to converge, and at 480 min after administration of the loading dose the concentrations predicted by the two models are identical. These simulations support our conclusion that CPB has minimal clinically relevant effects on sufentanil pharmacokinetics.

We have presented simulations for one dose regimen designed to produce near-maximal opioid effects before CPB while still permitting sufentanil concentrations compatible with adequate spontaneous ventilation at the end of surgery or shortly thereafter. The pharmacokinetics of sufentanil are linear over a wide dose range.[17] Therefore, concentrations achieved are directly proportional to dose. For example, with a loading dose of 20 μg, followed by an infusion of 33 μg/h until the start of CPB, and then infusing 6 μg/h until the end of surgery, the predicted concentrations would be exactly half those shown in figure 5.

Conclusions

The model that we entered into STANPUMP was based on concentration *versus* time data collected entirely before CPB.[6] Given the potential limitations of using a model derived solely from pre-CPB data, it is noteworthy that the mean measured sufentanil concentration of 0.15 ng/ml at the end of surgery was identical to the target concentration. This observation supports our conclusion that CPB has minimal clinically important effects on sufentanil pharmacokinetics.

The impact of CPB on the pharmacokinetics of alfentanil in children[4] and propofol in adults[5] has been previously reported. These investigators pioneered the application of population pharmacokinetic modeling techniques that allowed for step-changes in parameters at the start or end of CPB. In both these studies, models that allowed for changes in pharmacokinetic parameters at the start or end of CPB were selected as the "best" models. However, in assessing models, these investigators considered only log-likelihoods for model discrimination, whereas we assessed both log-likelihood and predictive ability. In the pediatric alfentanil study, the authors commented that the predictive accuracy of the CPB-adjusted model was only slightly better than the predictive accuracy of the simple unadjusted model, although no other analysis of predictive accuracy was reported.[4] We have also shown that CPB-adjusted models do not improve predictive accuracy when fentanyl is administered by TCI before, during, and after CPB.[18]

In other studies, we have shown that sufentanil concentrations of ~0.7 ng/ml produce near-maximal opioid effects in patients undergoing coronary artery bypass grafting before CPB and that concentrations less than 0.5 ng/ml are associated with the need for high concentrations of isoflurane to control hemodynamic responses to surgical stimulation.[9] At the end of surgery, concentrations <0.2 ng/ml are required to permit adequate spontaneous ventilation.[10] In the current study, we have demonstrated that target pre-CPB sufentanil concentrations in the range of 0.5 to 0.7 ng/ml can be achieved and maintained by a sufentanil TCI and that target concentrations compatible with spontaneous ventilation (mean, 0.15 ng/ml) can be achieved by the end of surgery. This was accomplished using a preliminary pharmacokinetic model based only on concentration *versus* time data collected before initiation of CPB data,[6] which strongly supports our conclusion that CPB has minimal clinically insignificant effects on sufentanil pharmacokinetics in adults.

Clinicians who use our simple model to predict sufentanil concentrations during cardiac surgery must be aware that the concentrations will be lower than predicted just after initiation of CPB, and higher than predicted just after separation from CPB. The changes in measured concentrations at the start of CPB are relatively small, ~25%. Furthermore, the simulations predict that when a constant infusion of sufentanil is continued after initiation of CPB, the sufentanil concentration begins to increase only 12 min after initiation of CPB. The observed increase in sufentanil concentrations just after separation from CPB was greater (almost 50%). However, the measured concentration decreased rapidly, so that by the end of surgery the concentration was equal to the last concentration measured during CPB and also equal to the TCI target concentration. The simulation also indicates that the postCPB increase in sufentanil concentration is very transient. Given the current emphasis on rapid recovery of ventilatory drive in patients undergoing cardiac surgery, it is probably most impor-

tant to control opioid concentrations precisely at the end of the operation.

Although we have not prospectively validated the predictive ability of our final model in a second series of patients, the results of this current study assessing the impact of CPB on sufentanil pharmacokinetics are consistent with our previous investigations of CPB and fentanyl kinetics.[18] In that study, neither CPB-adjusted modeling nor mixed effects modeling improved predictive accuracy compared to a simple model estimated with the naïve pooled data method, and this simple model had good predictive ability when tested prospectively. Therefore, we are confident that our models for sufentanil pharmacokinetics will also predict sufentanil concentrations in comparable patients undergoing cardiac surgery.

Optimal use of opioids in cardiac anesthesia requires that:

- opioid concentrations that easily control responses to surgical stimulation when supplemented with other anesthetics are reliably achieved and maintained,
- effective postoperative analgesia and transition to other analgesic methods such as intravenous morphine is provided, and
- unintended opioid-induced respiratory depression does not contribute to the need for postoperative respiratory support.

Achieving all of these objectives is inherently difficult because opioids have very steep concentration-response curves.[7] In combination with pharmacodynamic data, accurate and precise pharmacokinetic models, such as those that we have defined, provide the scientific foundation for designing dose regimens that can reliably and predictably achieve these goals.

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