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Cardiopulmonary Bypass Has Minimal Effects on the Pharmacokinetics of Fentanyl in Adults

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Background: **Although fentanyl has been widely used in cardiac anesthesia, no complete pharmacokinetic model that has assessed the effect of cardiopulmonary bypass (CPB) and that has adequate predictive accuracy has been defined. The aims of this investigation were to determine whether CPB had a clinically significant impact on fentanyl pharmacokinetics and to determine the simplest model that accurately predicts fentanyl concentrations during cardiac surgery using CPB.**

Methods: **Population pharmacokinetic modeling was applied to concentration-*versus*-time data from 61 patients undergoing coronary artery bypass grafting using CPB. Predictive ability of models was assessed by calculating bias (prediction error), accuracy (absolute prediction error), and measured:predicted concentration ratios *versus* time. The predictive ability of a simple three-compartment model with no covariates was initially compared to models with premedication (lorazepam *vs.* clonidine), sex, or weight as covariates. This simple model was then compared to 18 CPB-adjusted models that allowed for step changes in pharmacokinetic parameters at the start and/or end of CPB. The predictive ability of the final model was assessed prospectively in a second group of 29 patients.**

Results: **None of the covariate (premedication, sex, weight) models nor any of the CPB-adjusted models significantly improved prediction error or absolute prediction error, compared to the simple three-compartment model. Thus, the simple three-compartment model was selected as the final model. Prospective assessment of this model yielded a median prediction error of +3.8%, with a median absolute prediction error of 15.8%. The model parameters were as follows: V_1, 14.4 l; V_2, 36.4 l; V_3, 169 l; Cl_1, 0.82 l · min^{-1}; Cl_2, 2.31 l · min^{-1}; Cl_3, 1.35 l · min^{-1}.**

Conclusions: **Compared to other factors that cause pharmacokinetic variability, the effect of CPB on fentanyl kinetics is clinically insignificant. A simple three-compartment model accurately predicts fentanyl concentrations throughout surgery using CPB.**

DURING the past decade, rapid postoperative recovery and earlier tracheal extubation have become priorities in the anesthetic management of adults undergoing cardiac surgery. Maximizing the beneficial effects of opioids while also minimizing the duration of postoperative respiratory depression requires greater precision in administering opioids. Fentanyl is often given during anesthesia for cardiac surgery using cardiopulmonary bypass (CPB). Despite this widespread practice, the impact of CPB on the pharmacokinetics of fentanyl has not been fully investigated. Many factors, including hemodilution, hypothermia, nonphysiologic blood flow, and the CPB-induced systemic inflammatory response, have the potential to affect drug distribution and elimination.[1] The objectives of this investigation were to determine whether CPB had any clinically important effect on fentanyl pharmacokinetics and to define a pharmacokinetic model that accurately predicted fentanyl concentrations before, during, and after CPB in patients undergoing coronary artery bypass grafting. To achieve the first objective, we compared multiple models that allowed for step changes in pharmacokinetic parameters with initiation of or separation from CPB and then selected a " final" model using predefined criteria. A similar approach has been used to investigate the pharmacokinetics of alfentanil in children[2] and propofol in adults[3] undergoing surgery using CPB. To achieve the second objective, we prospectively verified the predictive ability of our final pharmacokinetic model in a second group of patients.

Materials and Methods

After approval of these studies by the University of Manitoba Biomedical Research Ethics Board (Winnipeg, Manitoba, Canada), informed consent was obtained from all patients. Predefined exclusion criteria included age greater than 80 yr; weight greater than 110 kg; baseline preoperative mean arterial pressure greater than 100 mmHg; previous cardiac surgery; emergency surgery; left ventricular ejection fraction less than 0.3 or severe left ventricular dysfunction as assessed by cineangiography, radionuclide ventriculography, or echocardiography; unstable angina requiring intravenous nitroglycerin or continuous electrocardiographic monitoring; alcohol or drug abuse; current use of sedative hypnotics or tricyclic antidepressants; previous adverse reaction to any of the study drugs; major neurologic deficit; malignant hyperpyrexia; and planned awake intubation. The demographics of the patients in the modeling group and the validation group were typical of patients undergoing coronary artery bypass grafting (table 1). All patients received their usual antianginal medications up to and including the morning of surgery.

Model Estimation

Patients received either 5 μg/kg oral clonidine (n = 29) or 40–60 μg/kg oral lorazepam (n = 32) for sedation

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Table 1. Demographics

	Modeling Group (n = 61)	Validation Group (n = 29)
Age, yr	62.6 ± 9.6	63.7 ± 10.2
Weight, kg	81.2 ± 13.5	80.4 ± 12.4
Male/female	48/13	23/6
Chronic medications		
β-Adrenoceptor antagonists	47 (77%)	23 (79%)
Calcium channel blockers	18 (30%)	5 (17%)
Angiotension-converting enzyme inhibitors	11 (18%)	11 (38%)
Long-acting nitrates	46 (75%)	24 (83%)

Data are presented as mean ± SD, or number of patients (%).

75–90 min preoperatively. Ringer's lactate, 7 ml/kg, was infused before induction of anesthesia. Fentanyl was administered to all patients by a target-controlled infusion (TCI), using the program STANPUMP.§ Pharmacokinetic parameters from preliminary studies[4] were entered into STANPUMP. The initial fentanyl target concentrations ranged from 4 to 8 ng/ml. Thirty minutes after initiation of CPB, the target fentanyl concentration was reduced to 1.5 ng/ml. After preoxygenation, the fentanyl TCI was started. Two minutes later, 3 mg/kg intravenous thiopental and 1 mg/kg intravenous succinylcholine were administered, and the trachea was intubated. Subsequently, vecuronium was used as needed for muscle relaxation. No other intravenous anesthetics or adjuvants were administered before or during CPB. Before CPB, the end-tidal isoflurane was titrated as needed to maintain heart rate and mean arterial pressure within 20% of the preoperative values. During CPB, isoflurane was administered *via* the oxygenator to maintain mean arterial pressure between 50 and 90 mmHg. 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. The CPB circuit was primed with 700 ml Ringer's lactate and 500 ml pentastarch 10%. After separation from CPB, isoflurane was titrated at the discretion of the attending anesthesiologist. Low-dose propofol infusions (1–4 $mg \cdot kg^{-1} \cdot h^{-1}$) were begun after sternal closure. The fentanyl TCI was discontinued at the end of surgery. Total doses of fentanyl ranged from 10.6 to 33.0 μg/kg.

Arterial fentanyl concentrations were measured in multiple samples from each patient. Nominal sampling times were skin incision, sternotomy, sternal lift, aortic dissection, just before initiation of CPB, 5 min after initiation of CPB, every 30 min after initiation of CPB for 2 h, every hour thereafter, and the end of surgery. The sampling durations ranged from 145 to 447 min. Serum fentanyl concentrations were measured by radioimmunoassay. The average intrasample coefficient of variation was 1.9%, and the average percent error of the assay was −6.2% for standard samples over a concentration range of 2–14 ng/ml. The measured fentanyl concentrations just before initiation of CPB, 5 min after initiation of CPB, and 30 min after initiation of CPB were compared using repeated-measures analysis of variance. An additional sample was drawn from 21 patients immediately after successful separation from CPB. The fentanyl concentrations measured in this immediate post-CPB sample, the last sample drawn during CPB, and at the end of surgery were compared using repeated-measures analysis of variance. The Tukey test was used for pair-wise comparisons if analysis of variance returned $P < 0.05$.

Population pharmacokinetic modeling (naive pooled data technique) was performed with NONMEM V (Globomax LLC, Hanover, MD). A total of 753 samples were used for pharmacokinetic modeling. Initially, parameters for a simple three-compartment model with no covariates were estimated. We then estimated parameters for models with sex, weight, or premedication (lorazepam or clonidine) as covariates. We compared these four models to select the base model for development of the CPB-adjusted pharmacokinetic models. Predefined criteria for acceptance of more complex models were (i) an increase in log likelihood of at least 2 for each additional parameter,[2,3,5] and (ii) a significant ($P < 0.05$) improvement in either the prediction error (PE) or the absolute prediction error (APE).‖ This was tested by calculating the median values of PE and APE for each subject (n = 61) and each model and comparing these with the Kruskal-Wallis test.

We then estimated the parameters for 18 alternative models, which were adjusted for CPB by allowing parameters to change when CPB was initiated and/or terminated. Each of the six parameters of the base model (V_1, V_2, V_3, Cl_1, Cl_2, and Cl_3) was allowed to change in the following manner: (i) at initiation of CPB (but remaining unchanged thereafter), (ii) at separation from CPB, or (iii) to have a unique value during CPB (changing at initiation of CPB but reverting to the pre-CPB value at separation from CPB).

To select the final pharmacokinetic model, these CPB-adjusted models were then compared to each other and to the base model according to the above predefined criteria. The final model was also assessed by graphic analysis of the measured:predicted concentration ratios *versus* time.

Model Validation

The final pharmacokinetic model was validated prospectively in a second group of 29 patients. These patients were enrolled into a study comparing the intraoperative clinical efficacy of a single bolus dose of fentanyl

§STANPUMP is available from its author, Steven L. Shafer, M.D. (Professor, Department of Anesthesia, Stanford University, Stanford, California), *via* the World Wide Web at http://anesthesia.stanford.edu/pkpd/.

‖PE = $([Fentanyl]_{meas} - [Fentanyl]_{pred}) \times 100\%/[Fentanyl]_{pred}$. APE is its absolute value.

to a fentanyl TCI. Other aspects of anesthetic management and the conduct of CPB were as described for the modeling group, with these exceptions: (i) all patients received 40 μg/kg oral lorazepam 75 min preoperatively, (ii) 4 mg/kg intravenous thiopental was administered for induction of anesthesia, and (iii) rocuronium was used for muscle relaxation during surgery.

The total doses of fentanyl ranged from 10.7 to 20.8 μg/kg. Arterial fentanyl concentrations were measured in samples drawn two to five times in each patient between induction of anesthesia and the end of surgery. The duration of sampling ranged from 78 to 335 min from the time the fentanyl TCI was started or the time the fentanyl bolus was injected. A total of 100 samples were available for validation of the pharmacokinetic model: 50 in the 14 patients who received fentanyl using the TCI and 50 in the 15 patients who received a single bolus dose of fentanyl.

The final pharmacokinetic model was validated in this group by comparing the concentrations predicted by the model and the measured concentrations and then calculating PE and APE, and also by graphic analysis of the measured:predicted concentration ratios *versus* time. Separate analyses were performed for each of the bolus and TCI subgroups and for the combined group. PE and APE in the subgroups were compared with the rank-sum test.

Comparison of Naive Pooled Data and Mixed-effects Modeling Techniques

Finally, we repeated the modeling sequence using mixed-effects modeling to estimate the parameters for the following: (i) a simple, three-compartment model (not adjusted for CPB) and (ii) 18 models adjusted for CPB (as described above in the Model Estimation subsection).

For mixed-effects modeling, a log-normal error model and first-order estimation method were used.

Results

The measured fentanyl concentrations just before initiation of CPB and 5 and 30 min after initiation of CPB in the modeling group are shown in figure 1, *left*. The mean concentrations at these three times were 5.7, 4.3, and 4.5 ng/ml, respectively. The pre-CPB concentrations were significantly different ($P < 0.001$) from the concentrations 5 and 30 min after initiation of CPB.

Figure 1, *right*, displays the last fentanyl concentrations measured during CPB, the concentrations immediately after separation from CPB, and at the end of surgery in the modeling group. The mean concentrations at these times were 2.0, 2.5, and 1.5 ng/ml, respectively. Pair-wise analysis indicated that the concentrations at each of these times were significantly different ($P < 0.001$) from the other two times.

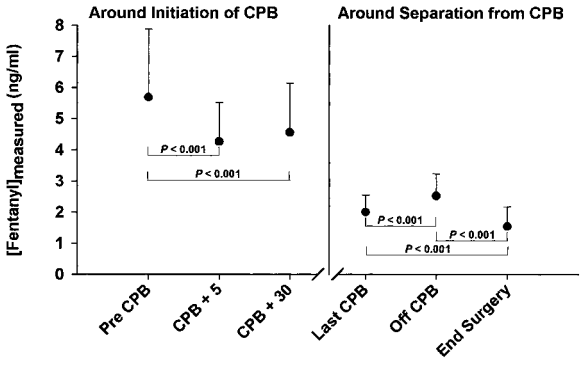

Fig. 1. The measured fentanyl concentrations (mean ± SD) around the times of initiation of cardiopulmonary bypass (CPB) (*left*: pre-CPB = just before initiation of CPB; CPB + 5 = 5 min after initiation of CPB; CPB + 30 = 30 min after initiation of CPB) and separation from CPB (*right*: last CPB = last sample drawn during CPB; off CPB = after successful complete separation from CPB).

Model Estimation: Base Model

The simple, three-compartment model with no covariates had an overall (n = 753) median PE of 0.8% (interquartile range, −17.6% to 20.7%), and the overall median APE (n = 753) was 18.6% (interquartile range, 8.6% to 33.5%). The overall PE, APE, and change in log likelihoods for the models with sex, weight, or premedication as covariates are shown in table 2. The models with either premedication or weight as covariates met the criterion of having an increase in log likelihood greater than 2, although these increases were modest (< 3). When the median values of PE and APE from each subject were compared, there were no significant differences in either PE or APE between any of these models ($P = 0.97$ for both PE and APE). Therefore, on the basis of our predefined criteria for model selection, the simple, three-compartment model was used as the base model for estimating CPB-adjusted models.

Model Estimation: CPB-adjusted Models

Compared to the base model, each of the six models that allowed one parameter to change at the start of CPB (remaining constant thereafter) increased log likelihood by greater than 2 (range, 3.9–20.8). Similarly, each of the six models that allowed one parameter to have unique value during CPB increased log likelihood by greater

Table 2. Comparison of Covariate Models

Covariate	PE, %	APE, %	Change in Log Likehood*
None	−0.8 (−17.6, +20.7)	18.6 (8.6, 33.5)	
Premedication	+0.05 (−18.4, +20.8)	19.3 (8.4, 32.7)	2.17
Sex	−0.9 (−17.5, +21.1)	19.1 (8.4, 33.1)	0.98
Weight	+0.7 (−16.9, +22.4)	18.8 (9.4, 33.1)	2.98

Median prediction error (PE) and absolute prediction error (APE) are shown with their respective interquartile ranges. There are no significant differences in PE or APE.

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

Table 3. Parameters of the Final Three-Compartment Model

Volumes, l			Clearances, l/min		
V_1	V_2	V_3	Cl_1	Cl_2	Cl_3
14.4	36.4	169	0.82	2.31	1.35

than 2 (range, 6.6–17.7). Of the six models that allowed a step change in a parameter at separation from CPB, only the model that allowed V_3 to change met the log-likelihood criterion, increasing log likelihood by 2.7. However, in comparing the median PE and APE from each subject for all of the 18 CPB-adjusted models and the base model, there were no significant differences in PE or APE ($P > 0.05$). The overall median PE (n = 753) for these models ranged from −1.8% to + 0.2%, compared to −0.8% for the base model. The overall median APE ranged from 18.0% to 19.0%, compared to 18.6% for the base model. Because none of these 18 CPB-adjusted models improved either median PE or APE, they failed to meet our criteria for selection of a more complex model, in preference to the base model. Therefore, we did not explore any models of greater complexity (allowing > 1 parameter to change and the start or end of CPB), and we selected the simple, three-compartment model, without covariates and without adjustments for CPB, as our final model. The parameters of this model are shown in table 3. The measured:predicted ratios for this model, using the concentration-*versus*-time data on which it is based, are shown in figure 2. No systematic time-related changes in bias is evident.

Median overall PE and APE for the simple, three-compartment model and the 18 CPB-adjusted models estimated using the naive pooled data technique are listed in table 4.

Model Validation

The PE and APE for the bolus subgroup, the TCI subgroup, and all patients in the validation group combined are shown in table 5. The median PE in the TCI subgroup was −5.7%, which was significantly different from the median PE in the bolus subgroup, +10.2%. The median PE after pooling these data was +3.8%. There was no difference in the APE between the two subgroups. The measured:predicted concentration ratios *versus* time for the validation group are shown in figure 3. No time-related changes in bias are apparent.

Naive Pooled Data versus *Mixed-effects Modeling*

Median overall PE and APE for the simple, three-compartment model and the 18 CPB-adjusted models estimated using the mixed-effects modeling are listed in table 4. As was the case when naive pooled data modeling was used, in comparing the median PE and APE from each subject using mixed-effects modeling, there were no significant differences in PE or APE ($P > 0.05$) between any of the 18 CPB-adjusted models and the base model. The data in table 4 indicate that, generally, the values for PE and APE from the mixed-effects models are greater than the corresponding value obtained by naive pooled data modeling—certainly, the predictive ability of the mixed-effects models is not systematically better than the predictive ability of the models estimated by the naive pooled data technique.

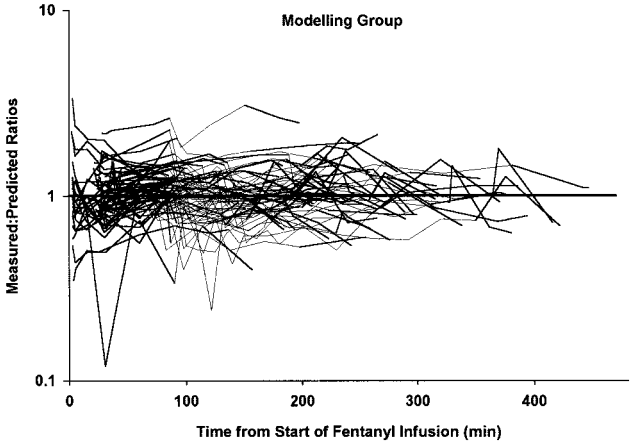

Fig. 2. The measured:predicted concentration ratios *versus* time, applying the final model to the data observed in the modeling group. Each *plot* represents data from one subject, and the *finer segment* of each plot indicates the time from the last sample before cardiopulmonary bypass to the last sample during cardiopulmonary bypass. The *thicker horizontal line* indicates perfect predictive ability (M:P ratio equal to 1 at all times).

Discussion

For more than two decades, fentanyl has been used in anesthesia for cardiac surgery. Despite this longstanding and widespread practice, no pharmacokinetic model that accurately predicts fentanyl concentrations during surgery using CPB and that has assessed the impact of CPB on fentanyl pharmacokinetics has been published. Our model provides anesthesiologists with the basic information needed to predict the fentanyl concentration–*versus*–time curve that any specific dose regimen will produce. Several freely available programs can be used to simulate these curves, after entering the parameters of a pharmacokinetic model, and any dose regimen of interest. # The current practice of cardiac anesthesia emphasizes rapid recovery of adequate respiratory drive and early tracheal extubation. Our model provides a scientific foundation for designing dose regimens that can maximize the benefits of opioids perioperatively, such as suppression of responses to noxious stimuli and effective postoperative analgesia, while minimizing the

Stanford PK/PD Software Server. Available at: http://anesthesia.stanford.edu/pkpd/. Maintained by Stephen L. Shafer, M.D. Accessed May 13, 2002. The Stanford PK/PD Software Server has several programs that can be downloaded and used to simulate concentration-*versus*-time curves. These are accessed through the Target Control Drug Delivery link.

Table 4. Median PE and APE for Naive Pooled Data and Mixed-effects Modeling Techniques

Model	Naive Pooled Data		Mixed-effects Modeling	
	Median PE (%)	Median APE (%)	Median PE (%)	Median APE (%)
Simple, three-compartment model, not adjusted for CPB	−0.81	18.61	−2.88	19.37
Parameter changes at start of CPB, no change at end of CPB				
Cl_1	−1.37	18.09	−1.89	18.19
Cl_2	−1.36	18.35	−2.41	18.95
Cl_3	−1.41	18.54	−0.43	19.30
V_1	0.16	18.18	−0.52	18.53
V_2	−1.01	18.24	−1.18	18.16
V_3	−1.38	18.51	−0.27	18.51
Parameter changes at start of CPB, reverts to pre-CPB value at end of CPB				
Cl_1	−0.50	18.40	−0.81	18.27
Cl_2	−1.36	18.75	−1.89	18.41
Cl_3	−1.78	18.28	−1.48	19.05
V_1	−0.26	18.19	−0.72	18.31
V_2	−0.80	18.00	−1.69	17.77
V_3	−0.50	18.64	−0.09	20.04
Parameter changes at end of CPB				
Cl_1	−0.73	18.68	−2.62	19.56
Cl_2	−0.88	18.59	−3.27	19.60
Cl_3	−0.69	19.00	−2.76	19.48
V_1	−0.80	18.75	−2.25	19.42
V_2	−0.64	18.58	−2.60	19.18
V_3	−0.53	18.89	−3.26	19.38

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

risk of prolonged postoperative respiratory depression. In combination with pharmacodynamic information, which relates drug concentrations to drug effects,[6,7] anesthesiologists now have the information needed to design fentanyl dose regimens for patients undergoing cardiac surgery to meet any desired therapeutic goals.

Measured Fentanyl Concentrations

The fentanyl concentrations measured 5 min after initiation of CPB were significantly lower that the pre-CPB concentration. This is expected because the priming solution of the CPB circuit expands the patient's blood volume, resulting in hemodilution. The decrease in mean fentanyl concentrations from 5.7 to 4.3 ng/ml represents a 25% change in concentration. Thirty minutes after initiation of CPB, the mean fentanyl concentration was 4.5 ng/ml, which was still significantly different from the pre-CPB concentration. During this period, the target fentanyl concentration entered into STANPUMP remained at the pre-CPB setting. Thirty minutes after the start of CPB, the target concentration was reduced to 1.5 ng/ml in all patients. This interrupts the TCI until the model entered into STANPUMP predicts that the concentration is approaching 1.5 ng/ml. The duration of this interruption is dependent primarily on the total dose of fentanyl administered before reducing the target concentration. In patients undergoing shorter surgeries, the fentanyl TCI would not be resumed before the end of surgery, because the concentration predicted by

Table 5. Predictive Ability of the Models in the Validation Group

	PE (%)	APE (%)
Bolus Subgroup	+10.2 (−8.9, +33.0)	19.5 (10.1, 37.0)
TCI Subgroup	−5.7 (−17.1, +12.2)	14.8 (8.8, 28.2)
Combined	+3.8 (−14.1, +20.6)	15.8 (9.3, 34.0)

Median prediction error (PE) and absolute prediction error (APE) are shown above their respective interquartile ranges.

TCI = target-controlled infusion.

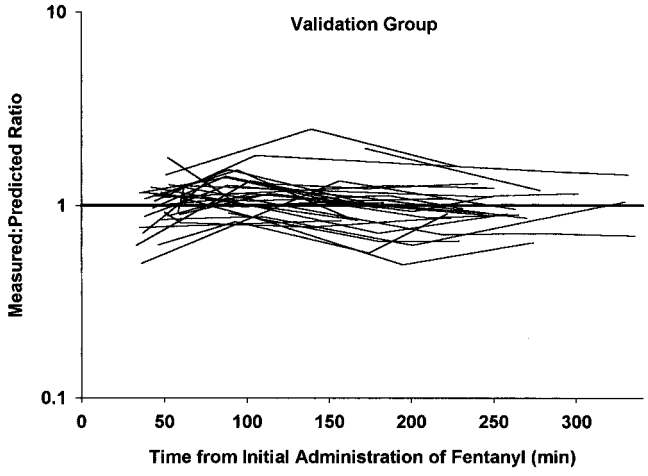

Fig. 3. The measured:predicted concentration ratios *versus* time, applying the final model to the data observed in the validation group. Each *plot* represents data from one subject. The *thicker horizontal line* indicates perfect predictive ability (M:P ratio equal to 1 at all times).

STANPUMP would not have decreased to 1.5 ng/ml before the end of surgery.

For assessment of the impact of initiating CPB on the measured concentrations of fentanyl, it would have been preferable to leave the target concentration at the pre-CPB setting for a longer period than 30 min after initiation of CPB. This would have allowed us to determine whether the measured concentrations would return to the pre-CPB levels. However, simulation of such TCI regimens indicated that the total dose of fentanyl would have been too large to be compatible with adequate spontaneous ventilation at the end of surgery or shortly thereafter. Prolonging the duration of postoperative opioid-induced respiratory depression in study patients was simply not practical, given our clinical resources.

Fentanyl concentrations measured just after separation from CPB were significantly greater than the last concentrations measured during CPB, 2.5 *versus* 2.0 ng/ml. This is a 25% increase in concentration. This is explicable by elution of fentanyl from the lungs with restoration of pulmonary blood flow during separation from CPB.[8] Just before initiation of CPB, the lungs were exposed to relatively high concentrations of fentanyl, averaging 5.7 ng/ml, and the lungs have considerable affinity for fentanyl and other lipophilic organic bases.[9] Improved perfusion of peripheral vascular beds with restoration of more physiologic and pulsatile blood flow after separation from CPB could also contribute to elution of fentanyl from tissues into the blood. However, as others have observed,[8] this is a very transient phenomenon. By the end of surgery, the mean measured fentanyl concentrations had decreased to 1.5 ng/ml, which was significantly lower than either the last concentration measured during CPB, or the immediate post-CPB concentration. The median measured concentration at the end of surgery was 1.4 ng/ml, very close to the target concentration setting of 1.5 ng/ml.

We measured total fentanyl concentrations in all samples, and thus did not assess any changes in binding of fentanyl to plasma proteins. Hemodilution at initiation of CPB will dilute free drug, protein-bound drug, and the binding proteins equally. Under such circumstances, the law of mass action dictates that the free fraction of drug will increase. This will offset 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.[10] Therefore, the 25% decrease in total fentanyl concentration we observed at initiation of CPB would have been accompanied by a lesser decrease in free fentanyl concentrations.

Model Estimation

Accurate and precise pharmacokinetic models provide a rational foundation for designing dose regimens that achieve and maintain desired target concentrations. To be useful clinically, a pharmacokinetic model must be virtually free of bias (median PE close to zero, without any time-related change in bias) and must have adequate precision (median APE of $< 30\%$).[11]

Our first step in pharmacokinetic modeling was to determine the parameters for a simple three-compartment model. This initial model was the benchmark against which more complex models that incorporated various covariates or adjustments for CPB were compared. An increase in log likelihood of greater than 2 (for each added parameter) has been used as the sole criterion for model discrimination[2,3,5]—the process of determining the simplest model that accurately describes the observed data. However, in terms of improved clinical usefulness, we believe that a pharmacokinetic model is better only if it significantly improves predictive ability by decreasing PE and/or APE. Therefore, in addition to meeting the log-likelihood criterion, we also stipulated that more complex models would also have to improve bias or precision (alternatively referred to as PE or APE, respectively).

When compared to the initial model, none of the models with premedication (lorazepam *vs.* clonidine), sex, or weight as covariates improved PE or APE, as tested by comparing median values of PE and APE for each subject. The is not surprising because the initial model had virtually no bias (overall median PE = -0.8%; n = 753) and a good degree of precision (overall median APE = 18.6%; n = 753), thus meeting the criteria for clinical utility.[11] This is consistent with our previous studies of distribution-phase sufentanil pharmacokinetics in patients undergoing coronary artery bypass grafting, which also showed that none of the covariates tested, including sex, weight, or concomitantly administered medications (lorazepam, morphine–scopolamine, clonidine, or propofol), significantly improved predictive ability.[12]

Similarly, although 13 of the 18 CPB-adjusted pharmacokinetic models that were tested met the log-likelihood criterion, comparison of the median values of PE or APE indicated that there were no significant differences between the initial base model and any of the 18 CPB-adjusted models. Therefore, we decided not to explore more complex models (allowing more than one parameter to change at the start and/or the end of CPB), and we chose the simple, three-compartment model, without any covariates or adjustments for CPB, as our final model.

Model Validation

The overall predictive ability of our final model in the validation group was excellent, with median PE of $+3.8\%$ and median APE of 15.8%. These are well within recommended criteria for clinical utility.[11] Furthermore, there was no evidence of time-related change in bias with graphical analysis. It is not surprising that in the model validation group, our final model (determined in patients given fentanyl by TCI) was better at predicting

fentanyl concentrations in the TCI subgroup, compared to the bolus subgroup. Pharmacokinetic models estimated from concentration-*versus*-time data collected during TCI have better predictive ability for subsequent drug administrations using TCI, compared to models developed using other modes of drug administration.[13]

Naive Pooled Data versus *Mixed-effects Modeling*

In our preliminary studies, we used the naive pooled data technique to determine a pharmacokinetic model for fentanyl in patients undergoing coronary artery bypass grafting using CPB.[4] Although this preliminary model was based only on fentanyl concentrations measured before CPB, it predicted concentrations during and after CPB quite well.[4] Therefore, we were confident that the naive pooled data technique would work well when concentration data for the entire operative period was used for pharmacokinetic modeling.

In nonmathematical terms, the difference between mixed-effects modeling and naive pooled data modeling can be summarized as follows: mixed-effects modeling partitions the residual error (the variability not explained by the model) into intersubject and intrasubject variability. In contrast, naive pooled data modeling does not attempt to identify the source of residual error in this way. Mixed-effects modeling is better in some situations, *e.g.*, when there are only very few observations (measured concentrations) in some subjects. However, the statistical complexity of mixed-effects modeling has a cost. PE and APE are almost invariably not as good (closer to 0 is better) when compared to naive pooled data modeling. We had a median of 11 observations in each subject. Also, the clinical utility of any pharmacokinetic model is its ability to accurately predict concentrations, hence our emphasis on PE and APE. For these reasons, we elected to use naive pooled data modeling primarily— our data set was suitable for this technique, and we anticipated that it would have better predictive accuracy, compared to mixed-effects modeling.

The relative merits of naive pooled data *versus* mixed-effects modeling are controversial.[14] Other investigators have compared these different modeling techniques in studies of various intravenous anesthetics in different patient populations.[15–17] These studies have failed to demonstrate any advantages of mixed-effects modeling, compared to less complex modeling methods. Their results are consistent with our comparison of naive pooled data and mixed-effects modeling (table 4). A fundamental principle of model discrimination is choosing the simplest model that adequately describes the data. Accordingly, we selected the simple, three-compartment model without any adjustments for CPB and determined using naive pooled data modeling, as our "final" model.

Conclusions

How can the observations of significant fluctuations in measured fentanyl concentrations at initiation of and separation from CPB be reconciled with the failure of any CPB-adjusted pharmacokinetic model to improve significantly predictive ability? The significant changes in the measured fentanyl concentrations just after initiation of and separation from CPB indicate that CPB does alter fentanyl pharmacokinetics. However, the observed changes in concentrations were relatively small, approximately 25%, and certainly after separation from CPB, very transient—the immediate post-CPB concentration of 2.5 ng/ml decreased rapidly to 1.5 ng/ml by the end of surgery. Fentanyl is a very lipophilic drug that is taken up extensively by tissues. This extensive tissue reservoir tends to buffer any acute decrease in the blood concentration of fentanyl, such as occurred with initiation of CPB. The large tissue capacity for uptake of fentanyl also buffers any acute increase in concentration, which explains the rapid decrease in concentration after the immediate post-CPB increase in the measured fentanyl concentrations. We conclude that because of these physicochemical properties, the potential impact of CPB on fentanyl blood concentrations is rendered insignificant in comparison to other random factors that cause pharmacokinetic variability. In other words, the signal (systematic changes in concentration at the start and end of CPB) is relatively small compared to the noise (random pharmacokinetic variability)—so that the signal-to-noise ratio of the effect of CPB on fentanyl pharmacokinetics small enough that we believe it can be ignored in clinical practice.

The inherent limitations of compartmental modeling may also have contributed to the inability of any CPB-adjusted model to improve predictive ability significantly. Drug disposition is a complex physiologic process that is affected by the magnitude of blood flow to the various tissues and organs in the body, the affinity of those tissues and organs for the drug, delivery of drug to organs capable of eliminating it, and the efficiency of elimination by those organs. Compartmental models are an oversimplification of the many physiologic processes that affect drug disposition. For example, because compartments cannot be equated with tissues, buffering of acute changes in the blood concentration by either uptake of fentanyl into or release of fentanyl from peripheral tissues is not likely to be adequately characterized by compartmental modeling.

The pharmacokinetic model that we entered into STANPUMP was based on preliminary studies using concentration-*versus*-time data collected entirely before CPB.[4] Considering the potential limitations of using a model derived solely from pre-CPB data, it is remarkable that the median measured fentanyl concentration at the end of surgery in the model estimation group was 1.4 ng/ml, which is within 7% of the target concentration at the end of surgery, 1.5 ng/ml. This observation provides strong sup-

port for our conclusion that CPB has minimal clinically important effects on fentanyl pharmacokinetics.

If our simple model is used to predict fentanyl concentrations during cardiac surgery, clinicians must recognize that the fentanyl concentrations will be lower than predicted for at least 30 min after initiation of CPB and higher than predicted just after separation from CPB. However, the changes in fentanyl concentrations at the start and end of CPB are relatively small, typically approximately 25%. Given the current emphasis on rapid recovery of ventilatory drive in patients undergoing cardiac surgery, it is arguably most important to control fentanyl concentrations precisely at the end of surgery. The post-CPB increment in fentanyl concentrations is transient, and by the end of surgery, the predicted and measured concentrations will be similar.

The effects of CPB on the pharmacokinetics of alfentanil in children[2] and propofol in adults[3] have been previously reported. These investigators developed the concept of applying population pharmacokinetic modeling techniques to models 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 by the investigators. However, these investigators used only log likelihood for model discrimination, whereas we used both log likelihood and predictive ability. In the pediatric alfentanil study, the authors comment that the predictive accuracy of the more complex CPB-adjusted model was only slightly better than the predictive accuracy of the simple unadjusted model (no statistical analysis of predictive accuracy was reported).[2] In comparing our study with theirs, we believe that our additional criterion of improved predictive ability accounts for the differences in the nature of the final model selected: simple *versus* CPB adjusted.

We have previously demonstrated that fentanyl concentrations of 7 ng/ml have near-maximal opioid effects in patients undergoing coronary artery bypass grafting and that concentrations lower than approximately 5 ng/ml are associated with the need for higher concentrations of volatile agents to control hemodynamic responses to intense surgical stimulation.[6] At the end of surgery, concentrations in the range of 2 ng/ml are required to permit adequate spontaneous ventilation.[7] In the current study, we have demonstrated that mean pre-CPB fentanyl concentrations of 5–6 ng/ml can be achieved and maintained by a fentanyl TCI and that concentrations compatible with spontaneous ventilation (mean, 1.5 ng/ml) can be achieved by the end of surgery. This was accomplished using a preliminary pharmacokinetic model based only on pre-CPB data.[4]

We believe that three therapeutic objectives need to be fulfilled to optimize use of intravenous opioids in patients undergoing cardiac surgery:

- achieving and maintaining opioid concentrations that effectively control responses to surgical stimulation when supplemented appropriately by a volatile anesthetic, without needing to administer vasodilators or β-adrenoceptor antagonists,
- providing effective postoperative analgesia, and
- minimizing the contribution of opioid-induced respiratory depression to the need for postoperative respiratory support.

Achieving all of these objectives is inherently difficult because of the typically steep concentration–response curves for opioids.[18] In combination with pharmacodynamic data, accurate and precise pharmacokinetic models, such as the one we have defined, provide the scientific foundation for designing dose regimens that can achieve these goals in a reliable and predictable manner.

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