Cardiothoracic Anesthesia, Respiration and Airway

Validation of fentanyl pharmacokinetics in patients undergoing coronary artery bypass grafting

[Validation de la pharmacocinétique du fentanyl utilisé pour un pontage aortocoronarien (PAC)]

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Purpose: The current emphasis on more rapid recovery and earlier tracheal extubation after cardiac surgery requires greater precision in administering opioids to reap their benefits while minimizing the duration of postoperative respiratory depression. Therefore, we aimed to define a pharmacokinetic model that accurately predicts fentanyl concentrations before, during, and after cardiopulmonary bypass (CPB) in patients undergoing coronary artery bypass grafting (CABG).

Methods: Parameters for two-compartment and three-compartment models were estimated by applying population pharmacokinetic modelling to fentanyl concentration vs time data measured in 29 patients undergoing elective, primary CABG. The ability of these models to predict fentanyl concentrations in a second series of ten patients undergoing CABG was then assessed.

Results: A simple, three-compartment model had excellent predictive ability, with a median prediction error ($PE = ([Fentanyl]_{meas} - [Fentanyl]_{pred})/[Fentanyl]_{pred} \cdot 100\%$) of -0.5% , and a median absolute PE ($APE = |PE|$) of 14.0% . In comparison to the two-compartment models, linear regression of measured:predicted concentration ratios indicated that the three-compartment model was free of systematic and time-related changes in bias ($P < 0.05$). The parameters of this three-compartment model are: V_1 15.0 l, V_2 20.0 l, V_3 86.1 l, Cl_1 1.08 L·min⁻¹, Cl_2 4.90 L·min⁻¹, and Cl_3 2.60 L·min⁻¹.

Conclusions: Our pharmacokinetic model provides a rational foundation for designing fentanyl dose regimens for patients undergoing CABG. When combined with previously published information regarding intraoperative fentanyl pharmacodynamics, dose

regimens that reliably achieve and maintain desired fentanyl concentrations throughout the intraoperative period can be designed to achieve specific therapeutic goals.

Objectif : L'accent mis actuellement sur une récupération plus rapide et une extubation endotrachéale précoce en cardiologie exige l'administration plus précise d'opioïdes. Nous pouvons ainsi en retirer les avantages tout en diminuant la durée de la dépression respiratoire postopératoire. Notre but était de définir un modèle pharmacocinétique prédictif précis pour les concentrations de fentanyl utilisées avant, pendant et après la circulation extracorporelle (CEC) chez des patients qui subissent un PAC.

Méthode : Les paramètres des modèles à deux et trois compartiments ont été estimés en appliquant une modélisation de population à la concentration de fentanyl en fonction du temps chez 29 patients devant subir une première intervention chirurgicale pour un PAC non urgent. La capacité de ces modèles à prédire les concentrations de fentanyl a été évaluée ensuite auprès d'une seconde série de dix patients subissant un PAC.

Résultats : Un modèle à trois compartiments a présenté une excellente valeur prédictive, avec une erreur de prédiction médiane ($EP = ([Fentanyl]_{mesuré} - [Fentanyl]_{prédit})/[Fentanyl]_{prédit} \cdot 100\%$) de $-0,5\%$, et une EP médiane absolue ($EPA = |EP|$) de $14,0\%$. En le comparant aux modèles à deux compartiments, la régression linéaire des ratios de la concentration mesurée:prédite a indiqué que le modèle à trois compartiments était exempt de biais systématiques et reliés au

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Supported by an operating grant from the Manitoba Medical Services Foundation. Drs. Henderson, Harding, and Peterson participated in this research during their University of Manitoba BSc (Medicine) Programs. They received salary support from the Pharmaceutical Manufacturers Association of Canada Research Foundation (Drs. Henderson and Peterson), the St. Boniface General Hospital Research Foundation (Dr. Harding), and the Medical Research Council of Canada (Dr. Peterson).

Accepted for publication November 1, 2001.

Revision accepted December 16, 2001.

temps ($P < 0,05$). Les paramètres de ce dernier modèle sont : V_1 15,0 l ; V_2 20,0 l ; V_3 86,1 l ; Cl_1 1,08 L·min⁻¹ ; Cl_2 4,90 L·min⁻¹ et Cl_3 2,60 L·min⁻¹.

Conclusion : Notre modèle pharmacocinétique donne un fondement rationnel à la préparation posologiques du fentanyl pour un PAC. Combinant les informations déjà publiées sur la pharmacodynamie du fentanyl peropératoire, nous pouvons préparer des schémas posologiques aux concentrations de fentanyl désirées et les maintenir fidèlement tout au long d'une opération.

FENTANYL is widely used in the anesthetic management of adults undergoing cardiac surgery. The current emphasis on more rapid recovery and earlier tracheal extubation requires greater precision in administering opioids to maximize their benefits (such as suppression of responses to noxious stimuli and postoperative analgesia) while minimizing the extent of postoperative respiratory depression. We have previously determined concentration-response relationships for fentanyl in patients undergoing coronary artery bypass grafting (CABG).¹ In addition to these pharmacodynamic data, pharmacokinetic models that accurately predict intraoperative fentanyl concentrations are required to provide a rational foundation for designing dose regimens that achieve these goals.² Accordingly, we defined a pharmacokinetic model for fentanyl in patients undergoing CABG. The ability of this model to predict fentanyl concentrations before, during, and after cardiopulmonary bypass (CPB) until the end of surgery was assessed prospectively in a second group of patients.

Methods

After approval of these studies by our Health Research Ethics Board, informed consent was obtained from all patients. Exclusion criteria were: previous CABG, left ventricular ejection fraction < 0.30, unstable angina requiring continuous electrocardiogram monitoring or *in* nitroglycerin, coexisting valvular heart disease, morbid obesity, chronic treatment with sedative-hypnotics, or drug or alcohol abuse. Demographics in both groups of patients were typical of patients undergoing CABG (Table I). All patients received their usual antianginal medications up to and including the morning of surgery. Fentanyl was administered to all patients with a target-controlled infusion (TCI) system, using the program STANPUMP.^a

TABLE I Demographics

	Modelling Group (n = 29)	Validation Group (n = 10)
Age (yr)	65.2 ± 9.7	62 ± 11.7
Weight (kg)	84.5 ± 11.9	78 ± 14.2
Male/Female	23/6	7/3

TABLE II Parameters of the three-compartment model

Volumes (l)			Clearances (L·min ⁻¹)		
V_1	V_2	V_3	Cl_1	Cl_2	Cl_3
15.0	20.0	86.1	1.08	4.90	2.60

Model estimation

The pharmacokinetics of fentanyl were determined in 29 patients enrolled in clinical investigations of opioid-based anesthesia for elective CABG (Modelling Group). The hemodynamic and pharmacodynamic results, and other clinical aspects of these investigations, have been reported separately.^{1,3} Pharmacokinetic models determined from preliminary studies were entered into STANPUMP. The target fentanyl effect-site concentrations ranged from 5 to 15 ng·mL⁻¹, and the total doses of fentanyl ranged from 17.0 to 54.9 µg·kg⁻¹. These dose regimens maintained stable fentanyl concentrations ranging from 6 to 25 ng·mL⁻¹ during the pre-CPB period.^{1,3}

All patients received lorazepam 60 µg·kg⁻¹ *po* 75 min preoperatively, and an infusion of Ringer's lactate 7 mL·kg⁻¹ before induction of anesthesia. Anesthesia was induced by initiating the fentanyl TCI, and administering propofol 1 mg·kg⁻¹, plus succinylcholine 1 mg·kg⁻¹. The target fentanyl concentration in each patient remained constant throughout the entire period prior to CPB. No other *in* anesthetics were administered. The fentanyl TCI was stopped two minutes after placement of the aortic purse-string suture. Isoflurane, ≥ 0.25% end-tidal concentration was administered for five minutes before skin incision, then subsequently titrated to maintain stable hemodynamics.

Arterial blood for measurement of serum fentanyl concentrations was sampled six to eight times in each patient between induction of anesthesia and placement of the aortic purse-string suture prior to insertion of the perfusion cannulas. Nominal sampling times were at the following intraoperative events: endotracheal intubation, skin incision, sternotomy, sternal lift, sternal spread, start of periaortic dissection, and at placement of the aortic purse-string suture. The durations of sampling ranged from 53 to 150 min

a STANPUMP is available from the author: Steven L. Shafer, MD, Department of Anesthesia, Stanford University Medical Center H3580, Stanford, California 94305, USA.

(median 86 min). A total of 208 fentanyl concentrations were measured by radioimmunoassay (Janssen Biotech, Olen, Belgium). The average intrasample coefficient of variation was 2.7%, and the average percent error of the assay was 3.1% for standard samples in the range of 5–20 ng·mL⁻¹. Population pharmacokinetic modelling (naïve-pooled data technique) was done with NONMEM V (GloboMax LLC, Hanover, MD, USA). Initially, parameters for a two-compartment model were estimated. We then estimated parameters for two-compartment models with gender or weight as covariates, and for a three-compartment model without covariates. The predictive ability of these models in these 29 patients was assessed by comparing their log-likelihood values,⁴ prediction error (PE) or bias,^b and the absolute PE (APE) or precision (using the Kruskal-Wallis test).

Model validation

The ability of the two-compartment and three-compartment models to predict fentanyl concentration was assessed prospectively in a second group of ten patients (validation group). Anesthetic management including premedication was identical to the modelling group, except that thiopental 3 mg·kg⁻¹ was used for induction. The target fentanyl effect-site concentration was initially 6 ng·mL⁻¹; 30 min after initiation of CPB, the target concentration was reduced to 1.5 ng·mL⁻¹. The total fentanyl dose (mean ± SD) was 18.6 ± 2.4 µg·kg⁻¹. Prior to CPB, isoflurane was titrated as needed to maintain stable hemodynamics. During CPB, isoflurane was administered as required to maintain mean arterial pressure between 50 and 90 mmHg. After CPB, the end-tidal isoflurane concentration was maintained ≥ 0.5% until sternal closure. At this time, isoflurane was discontinued and a propofol infusion was begun (1–6 mg·kg⁻¹·hr⁻¹). CPB was conducted using mild hypothermia (core temperature ≥ 33°C), pulsatile flow, α-stat pH management, and non-silicone membrane oxygenators.

Arterial blood for measurement of serum fentanyl concentrations by radioimmunoassay was sampled nine to 13 times in each patient (total 106) between induction of anesthesia and the end of surgery. Nominal sampling times were at the following events: skin incision, sternotomy, sternal lift, aortic dissection, immediately before CPB, five minutes after the initiation of CPB, every 30 min after the initiation of CPB for two hours, every hour thereafter, and at the end of surgery. The sampling period ranged from 177 to 394

min (> 6.5 hr), with a median of 208 min. The average intrasample coefficient of variation was 1.9%, and the average percent error of the assay was -6.2% for standard samples in the range of 2–14 ng·mL⁻¹.

The ability of the models derived in the modelling group to predict the concentrations observed in the validation group was then assessed by comparing PE and APE (rank sum test), and by testing for systematic or time-related bias of the measured:predicted concentration ratios (linear regression). Null hypotheses were rejected when $P < 0.05$.

Results

Model estimation

The two-compartment model had a median (25th percentile, 75th percentile) PE of -1.0% (-13.0%, 14.5%), and a median APE of 14.0% (6.0%, 30.0%). Adding gender as a covariate did not result in any significant differences in log-likelihood, PE or APE. Allowing clearances and volumes to vary according to patient weight significantly worsened log-likelihood, although PE and APE were not significantly changed. Compared to the two-compartment model, the three-compartment model had a smaller PE of -0.5% (-13.5%, 14.0%), which was not statistically significant; an identical APE: 14.0% (6.0%, 28.5%); and did not have a significant improvement in log-likelihood. We chose to validate prospectively only the simple two-compartment and three-compartment models, because none of the more complex covariate models improved predictive ability.

Model validation

When the predictive ability of the two-compartment and three-compartment models was compared, there were no significant differences in PE or APE. However, linear regression of the measured:predicted concentration ratios *vs* time demonstrated that the three-compartment model had better predictive ability. The measured:predicted concentration ratios *vs* time for the two-compartment model are shown in Figure 1. Beyond 200 min, the measured concentrations become systematically greater than the predicted concentrations. The slope of the linear regression equation was greater than zero ($P < 0.001$), indicating a time-related change in bias. Also the 95% confidence interval for the intercept did not include 1, an indicator of systematic bias.

The measured:predicted concentration ratios *vs* time for the three-compartment model are shown in Figure 2. No time-related bias is evident visually. This was confirmed by regression analysis: the slope of the linear regression equation was not statistically different from zero, and the 95% confidence interval for the

b PE = $\frac{([Fentanyl]_{meas} - [Fentanyl]_{pred}) \cdot 100\%}{[Fentanyl]_{pred}}$.
APE is its absolute value.

FIGURE 1 The measured:predicted concentration ratios plotted against the time from the start of the infusion, using the two-compartment model to predict concentrations in the validation group. Each plot represents the data from one patient; the fine segment of each plot indicates the period between the last datum prior to CPB and the first datum after CPB. The solid horizontal bar indicates a measured:predicted ratio of one (zero bias). After 200 min, the measured concentrations are consistently greater than predicted. This time-dependant change in bias was statistically significant (see text).

FIGURE 2 The measured:predicted concentration ratios plotted against the time from the start of the infusion, using the three-compartment model to predict concentrations in the validation group. Each plot represents the data from one patient; the fine segment of each plot indicates the period between the last datum prior to CPB and the first datum after CPB. The solid horizontal bar indicates a measured:predicted ratio of one (zero bias). No time-dependant change in bias is evident visually, which was confirmed by linear regression analysis (see text).

intercept includes 1, indicating no systematic or time-related bias. The volumes and clearances of the three-compartment model are shown in Table II.

Discussion

Until the mid-1990s, administration of large doses of opioids was a widespread practice in cardiac anesthesia. The current emphasis on rapid recovery and early tracheal extubation requires greater precision in administering opioids to reap their benefits (such as suppression of responses to noxious stimuli and post-operative analgesia) while reducing the duration of unintended postoperative respiratory depression.

We have previously determined fentanyl concentration-response relationships prior to CPB in patients undergoing CABG. When appropriately supplemented with isoflurane, serum fentanyl concentrations of $\sim 7 \text{ ng}\cdot\text{mL}^{-1}$ have near-maximal opioid effects, and provide effective hemodynamic control without the need for vasodilators or β -adrenoceptor blockers.¹

Accurate and precise pharmacokinetic models are required to design dose regimens that achieve and maintain desired target drug concentrations. To be clinically useful, a pharmacokinetic model must be free of bias (median PE close to zero, and no time-related

change in bias), and must have a median APE of $< 30\%$.⁵ Our simple three-compartment model without covariates meets these criteria. The 15th and 85th percentiles for the APE of our model are -21% and $+33\%$, respectively. This means that the measured concentration is within 33% of the predicted concentration more than 70% of the time. This finding supports the excellent predictive ability of the three-compartment model.

Traditionally, log-likelihood has been the sole criterion for model discrimination,⁴ to select the simplest model that accurately describes the observed data. However, in a utilitarian sense, a model is “better” only if it improves predictive ability. Therefore, we feel that more complex models can be justified only if they improve predictive ability. More complex models with gender or weight as covariates did not improve predictive ability. Given the excellent predictive ability of the models without covariates, this is not unexpected. Compared to the two-compartment model, adding a third compartment improved predictive ability in the validation group, as evidenced by the absence of any systematic or time-related bias in the measured:predicted concentration ratios. Therefore, we chose the simple three-compartment model as our final model.

Our pharmacokinetic model was developed using fentanyl concentration *vs* time data collected entirely prior to CPB. It is noteworthy that this model accu-

rately predicts fentanyl concentrations during and after CPB. This suggests that in adults, CPB, at least as managed in our validation group, does not have a clinically important effect on fentanyl pharmacokinetics. The effects of CPB on the pharmacokinetics of propofol (in adults)⁶ and alfentanil (in children)⁷ have been investigated. In both these studies, models that allowed step-changes in pharmacokinetic parameters at initiation of CPB or at separation from CPB were selected as the best models by the investigators. In the pediatric alfentanil study, 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).⁷ One interpretation of the similar predictive accuracies of these two models is that CPB had minimal or no clinically significant effects on alfentanil pharmacokinetics, which would be consistent with the results of our study.

Pharmacokinetic parameters should generally not be used to predict drug concentrations for periods longer than the sampling duration on which the model is based. One of the few exceptions to this principle is when prospective validation demonstrates adequate predictive ability for longer periods, as was done in this study. We demonstrated good predictive accuracy during and after CPB, up to the end of surgery. However, our pharmacokinetic model should not be used to predict fentanyl concentrations in the postoperative period. This does not diminish its utility in the context of current clinical practice. Having opioid concentrations at the end of surgery (or shortly thereafter) that are compatible with adequate spontaneous ventilation is a prerequisite for earlier tracheal extubation. Our model provides a scientific basis for designing dose regimens for fentanyl that can achieve this goal.

In summary, we have determined a pharmacokinetic model that accurately predicts fentanyl concentrations throughout surgery in patients undergoing CABG throughout surgery. In combination with intraoperative fentanyl pharmacodynamic data,^{1,3} anesthesiologists now have a rational foundation for designing fentanyl dose regimens that could maximize the benefits of opioids during surgery, while being compatible with early tracheal extubation.

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