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Application of Physiologic Models to Predict the Influence of Changes in Body Composition and Blood Flows on the Pharmacokinetics of Fentanyl and Alfentanil in Patients

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Background: **The influence of changes in the physiologic state of a patient on the disposition of fentanyl and alfentanil is poorly understood. The aims of this study were to determine whether physiologic pharmacokinetic models for fentanyl and alfentanil, based on data from rats, could predict plasma concentrations of these opioids in humans and to determine how changes in physiology would influence the predictions of their disposition.**

Methods: **The predictions of the models were tested against plasma concentration data from published pharmacokinetic studies. The influences of changes in body composition, cardiac output, and regional blood flows on the disposition of the opioids were simulated.**

Results: **The models could predict independently measured plasma concentrations of the opioids after short infusions in humans. Simulations then predicted that differences in body composition between men and women would have little influence on the pharmacokinetics of the opioids. Changes in cardiac output would affect drug redistribution, and consequently the early decay of the plasma concentrations, but not markedly influence rates of elimination. Further, the clearance of the opioids would decrease and their volumes of distribution increase with the age of the patient, but this would only marginally affect the early disposition of the drugs. Even large fluctuations in peripheral or hepatic blood flows would have modest effects on arterial plasma concentrations of the opioids, and sudden "postoperative" increases in peripheral blood flows would cause minor secondary plasma concentration peaks.**

Conclusions: **The ability of the physiologic models to predict plasma concentrations of fentanyl and alfentanil in humans was confirmed. When changes in physiologic condition were simulated, effects on the pharmacokinetics of the opioids with possible implications for dosing were obtained only if cardiac output was varied over a wide range. (Key words: Aging; computer simulations; intravenous anesthetics; opioids; variability.)**

This article is featured in "This Month in Anesthesiology." Please see this issue of ANESTHESIOLOGY, page 4A.

FENTANYL and alfentanil are synthetic opioids that are widely used to supplement general anesthesia. The clinical response to given doses of opioid varies considerably, and this is at least in part a result of variability in disposition. Consequently, the influence of several factors, such as the patient's age,[1-10] sex,[4,7,9] body weight,[4,8] cardiac output,[11] or type and duration of surgery and anesthesia,[3,4,10] on the pharmacokinetics of the opioids have been investigated. Such studies normally use a two- or three-compartment mamillary model to interpret the data and therefore describe inter-individual differences in drug disposition in pharmacokinetic terms, for instance variations in clearance (CL), volume of distribution at steady state (V_{dss}), volume of the central compartment (V_c), or in various half-lives. It is not clear how changes in these parameters relate to the underlying variations in the physiologic condition of the patients. Nor is it always clear when and how changes in physiology may have clinically important effects on peak plasma concentration and early drug disposition after an intravenous bolus injection or short infusion of fentanyl or alfentanil.

Another problem is that mamillary models are time invariant, which means that all parameters of drug disposition, such as clearance, are assumed to remain con-

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stant during the study, although the assumption of time invariance is questionable. Anesthesia and surgery may influence physiologic factors (cardiac output, regional blood flows, renal and hepatic function, and so forth)[12-14] that govern distribution and elimination of drugs. Thus, secondary peaks and other transient changes in plasma concentration curves are commonly observed.[1,3,10,15-21] A conventional pharmacokinetic model normally ignores these deviations, by fitting a smooth curve through any irregularities in measured drug concentrations.

Physiologic pharmacokinetic models, on the other hand, are representations of the human (or animal) body in which organs and tissues are characterized by their respective volumes and blood flows. The influence of changes in these parameters on plasma concentrations of drugs therefore can be directly predicted. Until techniques for detailed study of tissue concentrations of drugs in humans are available, physiologic models must rely heavily on data gathered in animals. Therefore, their predictions must be verified as far as possible by comparison to actual plasma concentration data measured in humans.

We recently presented principles and applications of a physiologic model for thiopental in humans based on plasma and tissue concentration data obtained in rats[22] and identified cardiac output as an important determinant of the early disposition of this drug. The aims of the present study were to determine whether similar models could predict plasma concentrations of fentanyl and alfentanil in patients having surgery and to investigate the influence of various changes in physiologic state on the predicted disposition of these two opioids.

Methods

The physiologic models were created using blood and tissue concentration data obtained in rats.[23-25] They were scaled from animal to human physiologic features by substituting human values for blood flows, organ weights, and great vessel blood volumes.[22,25] Figure 1 shows the model structure. The models were set up using the SIMULINK and MATLAB software (MathWorks, Natick, MA) on a 486-based personal computer.[22,25] Because of previously described[25] problems in characterizing the disposition of alfentanil in the rat lung, parameters for the pulmonary disposition of this drug were calculated by moment analysis of arterial

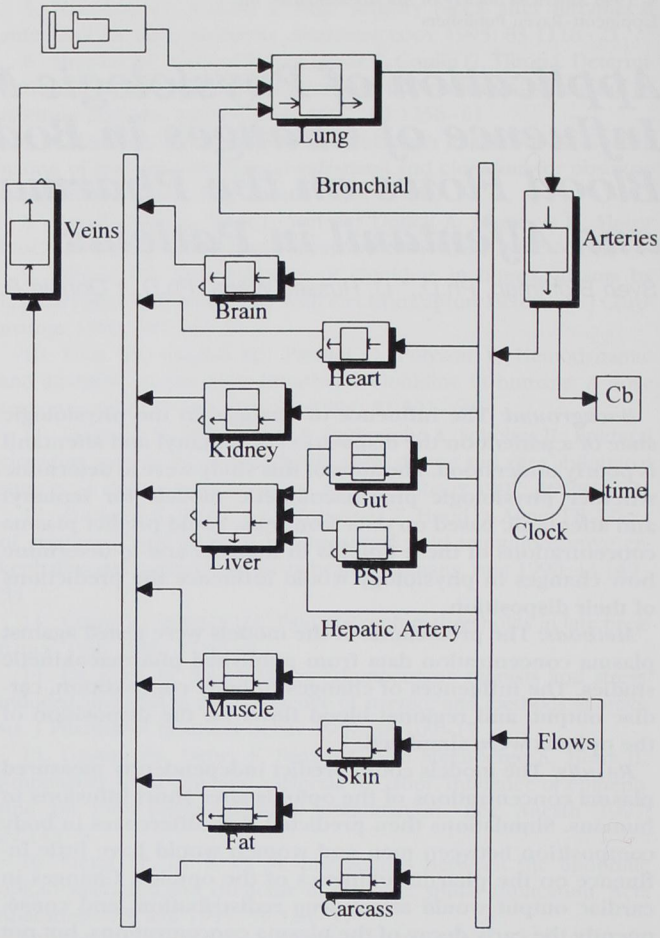

Fig. 1. The physiologic pharmacokinetic model for fentanyl and alfentanil in humans. The model consists of tissues, represented by one-, two-, or three-compartment submodels, and blood pools connected *via* the vasculature. "Lung" is a one-compartment model for fentanyl and a two-compartment model (as shown) for alfentanil. The "clock" generates simulation times corresponding to the simulated blood and tissue concentrations. Regional blood flows are generated in the box in the lower right-hand corner and add up to cardiac output. Some anatomic simplifications were made. Peripheral venous injection and peripheral arterial sampling are assumed to be indistinguishable from the illustrated central venous injection and aortic sampling (Cb), after consideration of appropriate transport delays. The entire gastrointestinal canal is represented as "gut." The pancreas and spleen are represented as a common tissue, "PSP."

blood concentrations of alfentanil after a single passage through the human lung[26] (data courtesy of Dr. K. Taeger, Munich, Germany).[27]

Table 1 shows organ weights and blood flows for a healthy man and woman. The weight of capillary blood has been added, as described,[22] to the reference weights of organ parenchyma.[28] In addition, values for a "hu-

Table 1. The Physiological Data Used to Define the Models

Organ/Tssue	Normal Man		Normal Woman		Normal "Human"			
	Weight (kg)	Blood Flow (ml/min)	Weight (kg)	Blood Flow (ml/min)	Weight (kg)	Blood Flow (ml/min)	$V_{app}F$ (l)	$V_{app}A$ (l)
Lungs	0.98	190*	0.77	150*	0.87	170*	18.2	2.17
Heart	0.45	260	0.37	270	0.41	270	2.3	0.28
Brain	1.44	780	1.24	670	1.34	730	7.6	0.34
Kidneys	0.36	1,240	0.32	960	0.34	1,100	4.6	0.35
Liver	2.47		1.92		2.19		19.6	3.15
Hepatic artery		450		350		400		
Gut	1.24	1,000	1.17	940	1.21	970	11.7	0.96
Spleen + pancreas	0.31	270	0.26	230	0.28	250	6.3	0.26
Muscle	30.8	1,140	18.5	680	24.6	910	71.2	7.29
Skin	3.36	400	2.34	280	2.85	340	9.4	1.02
Fat	12.7	350	17.8	490	15.3	420	428	37.8
Carcass	15.8	720	13.5	680	14.6	690	48.4	5.26
Great vessel blood	3.04		1.83		2.44		2.4	2.44
Total	73.0	6,800	60.0	5,700	66.5	6,250	630	61.3

$V_{app}F$ and $V_{app}A$ are the apparent volumes of distribution of fentanyl and alfentanil, respectively, in the organ/tissue.

* Bronchial artery.

man" were created by taking the mean of the data. Table 1 also shows the apparent volumes of distribution (V_{app}) of the two drugs in the organs. Each V_{app} was calculated as the sum of the apparent compartmental volumes for the opioid in this organ.[24,25]

The volumes of distribution at steady state (V_{dss}) of the two opioids were calculated as the sums of all V_{app} values in the healthy "man," "woman," and "human." Because these volumes refer to partitioning of drug between tissues and whole blood, the corresponding V_{dss} values for plasma as the reference medium were calculated as V_{dss} (plasma) = V_{dss} (blood) multiplied by the blood-to-plasma concentration ratio.

The predictions of the models were tested by comparison with original data from two studies of fentanyl,[3,29] with samples for drug assay drawn from the arterial circulation, and from two studies of alfentanil[2,30] with sampling from central venous catheters. For each participant, the rate and duration of the infusion were used as input to the model simulation, and the experimentally determined hepatic clearance (CL_{hep}) in each person was used to calculate intrinsic hepatic blood clearance (CL_{10}) per weight of liver tissue, according to the standard equation

$$CL_{hep} = \frac{Q_{hep} \cdot CL_{10}}{Q_{hep} + CL_{10}} \quad (1)$$

where Q_{hep} is total hepatic blood flow. Because relatively short blood sampling in the fentanyl studies may have given poor estimates of areas under the plasma concentration curves and thus also of clearance, predictions based on lower values were also tested. The prediction error was calculated as

$$PE = 100 \times \frac{C_m - C_p}{C_p} \quad (2)$$

where C_m and C_p are measured and predicted plasma concentrations, respectively. In fentanyl study I[3], the data were from 10 patients, 9 men and 1 woman, who weighed 79 ± 14 kg and were aged 67 ± 9 yr. Fentanyl (100 μg/kg) was given over 2 min to induce anesthesia for abdominal aortic surgery. Organ weights and blood flows for a man aged 67 yr, with an extra 5 kg of fat, were used for the simulations. In fentanyl study II[29], the data were from eight patients, three men and five women, whose mean weight was 68 kg and mean age was 45 yr. Fentanyl (150 μg/min) was infused for 5 min (in seven patients) or 6.5 min (in one patient). General anesthesia for spinal surgery then was induced with thiopental. Organ weights for a healthy "human" were used for the simulations. In alfentanil study I[2], the data were from nine young (three men, six women; mean weight, 70 ± 16 kg; mean age, 36 ± 7 yr) and 14 elderly (five men, nine women; mean weight, 66 ± 11 kg; mean age, 77 ± 7 yr) patients. General anesthesia for intra-abdominal surgery was induced with etomidate, and 50

μg/kg alfentanil was injected. In alfentanil study II[30], the data were from eight patients, five men and three women whose mean weight was 71 ± 9.1 kg and mean age was 47 ± 16 yr. General anesthesia for various types of major surgery was induced with thiopental, and 50 or 125 μg/kg alfentanil then was given as a bolus injection. Organ weights for healthy "humans" (aged 35 or 75 yr, as applicable) were used for all simulations of alfentanil pharmacokinetics.

In all further simulations, the values of hepatic CL_{10} were 0.51 $l \cdot min^{-1} \cdot (kg\ of\ liver)^{-1}$ for fentanyl and 0.36 $l \cdot min^{-1} \cdot (kg\ of\ liver)^{-1}$ for alfentanil. With blood-to-plasma concentration ratios of 1 for fentanyl and 0.63 for alfentanil,[31] this corresponds to apparent plasma clearances of 10 and 5 $ml \cdot min^{-1} \cdot (kg\ bodyweight)^{-1}$, respectively, in healthy humans, which is in general agreement with published findings.[2-5,8-11,19,20,30] By holding CL_{10} constant, the influence of changes in liver blood flow and liver weight on apparent elimination clearance can be predicted.

The general disposition (redistribution and elimination) of fentanyl and alfentanil was characterized in the healthy human, using predicted concentrations and amounts of drug *versus* time in all major organs and tissues as output from the physiologic model. In addition, total first-pass extraction in the systemic circulation was calculated.[25] The influence of changes in physiologic state on the pharmacokinetics of the opioids were then predicted for (1) the difference in average body composition between men and women; (2) a stable increase or decrease in basal cardiac output in a healthy young adult; (3) physiologic effects of aging in healthy humans; (4) fluctuations in hepatosplanchnic blood flow, affecting hepatic clearance of the drugs, with or without concomitant fluctuations in peripheral blood flows; and (5) sudden large changes in cardiac output and peripheral blood flows with the potential to cause secondary peaks in the plasma concentration curve. The simulated dosage of fentanyl was either a single intravenous injection of 10 μg/kg fentanyl (as free base) given over 1 min or, in simulations 4 and 5, this injection was immediately followed by a maintenance infusion of 0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 4 h. The dosage of alfentanil was 100 μg/kg by injection and 1.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ as a maintenance infusion. Details of the simulations are as follows.

Model Predictions

Sex. Table 1 shows regional blood flows and body compositions for a man and a woman.

Cardiac Output. Stable elevations or reductions in cardiac output were produced by changing regional blood flows (table 2). Myocardial, hepatosplanchnic (*i.e.*, hepatic arterial, "gut" and spleen plus pancreas), fat, and carcass blood flows were changed in direct proportion to cardiac output.[12,32,33] Muscle blood flow[34,35] was allowed to vary between 7.9 and 86 $ml \cdot min^{-1} \cdot kg^{-1}$ and skin blood flow[36] between 23 and 268 $ml \cdot min^{-1} \cdot kg^{-1}$. Blood flows to lungs (bronchial artery) and kidneys were kept constant, except when the very low cardiac output of 3.13 l/min was simulated. Then these blood flows were also decreased in proportion to cardiac output. Cerebral blood flow was never changed.

Aging. The assumed differences in body composition and blood flows among a 35-, 70-, and 90-yr-old human were as previously described.[22] Compared with the 35 yr old, adipose tissue mass was increased by 9% per decade. Liver mass was decreased for patients older than 55 yr by 9% for every 10 yr in excess of 55 yr. Muscle mass was decreased to maintain body weight at 67 kg. Specific blood flows, measured in milliliters per minute per organ weight (kg), to adipose tissue, hepatosplanchnic organs, brain, and kidney were decreased by 5%, 8%, 8%, and 12% per decade, respectively. Coronary blood flow was changed in proportion to cardiac output. Specific blood flows to muscle, skin, and remaining organs were not changed. The net effect on cardiac output was a decrease to 4.9 l/min at 70 yr and 4.2 l/min at 90 yr.

Fluctuating Hepatic Blood Flow. Two types of simulations were performed. In the first type, hepatosplanchnic blood flow fluctuated by ±50% of the baseline value, with the entire cycle (baseline, +50%; baseline, −50%; baseline in a sine wave pattern) lasting 15, 30, 60, or 120 min. This led to a fluctuation in cardiac output of ±0.81 l/min (±13%). In the second type of simulation, there were ±50% fluctuations in blood flows also in the muscle, fat, skin, carcass, and heart compartments, leading to variations in cardiac output of ±2.14 l/min (±34%).

Sudden Change in Cardiac Output. Cardiac output was increased from 4.69 to 7.81 l/min at different times after administration of fentanyl or alfentanil, with changes in regional blood flows as shown in table 2.

Results

The calculated V_{dss} of fentanyl was 8.07 l/kg in "man," 11.2 l/kg in "woman," and 9.47 l/kg in the "human"

Table 2. Changes in Peripheral Blood Flows and Cardiac Output (CO) Used for Simulations in the "Human" Model

Organ/Tissue	Blood Flow (ml/min) at: CO −50% (3.13 l/min)	CO −25% (4.69 l/min)	CO Normal (6.25 l/min)	CO +25% (7.81 l/min)	CO +50% (9.38 l/min)
Lung (bronchial artery)	85	170	170	170	170
Heart	135	205	270	340	405
Brain*	730	730	730	730	730
Kidneys	550	1,100	1,100	1,100	1,100
Liver					
Hepatic artery	200	300	400	500	600
Gut	490	730	970	1,215	1,455
Spleen + pancreas	125	190	250	315	380
Muscle	195	305	910	1,485	2,110
Skin	65	115	340	550	765
Fat	210	315	420	525	630
Carcass	345	520	690	865	1,040

* Blood flow not changed.

model. Because the blood-to-plasma concentration ratio of fentanyl is 1.0, these values are applicable to blood and plasma as the reference medium. The calculated V_{dss} of alfentanil, referenced to plasma, was 0.51 l/kg in "man," 0.67 l/kg in "woman," and 0.58 l/kg in the "human" model.

Comparisons of model predictions to literature data are shown in figure 2. In fentanyl study I, the total prediction error was 5.2 ± 33% (mean ± SD), after reduction of the clearance by 16% compared with experimental values. Per subject, the mean prediction errors ranged from −10% to 33%. In study II, fentanyl concentrations were measured for relatively short times (only 8 h in some patients), and an overall prediction error of 8 ± 42% was obtained by setting the clearance in the model 38% lower than the measured values. Mean prediction errors per subject ranged from −27% to 55%. In alfentanil study I, the overall prediction error was −2.1 ± 35%, with mean prediction errors per participant ranging from −15% to 10%. Similar results (data

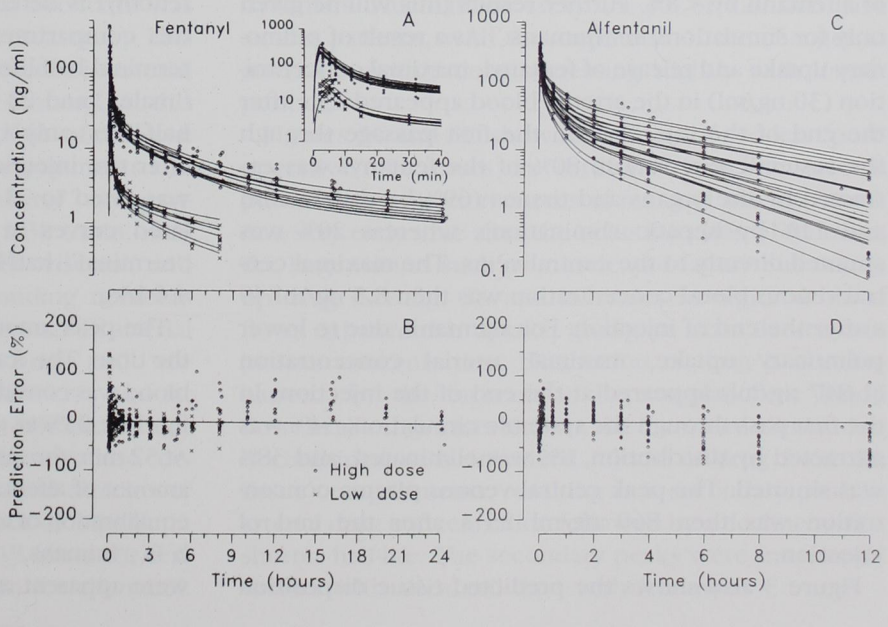

Fig. 2. (*A*) Model-predicted arterial plasma concentration curves and measured concentrations of fentanyl in study I[3] (high dose) and in study II[29] (low dose). (*B*) Prediction error *versus* time for the two studies. Early prediction errors tended to be negative in study I but positive in study II. (*C*) Model-predicted central venous plasma concentration curves and measured concentrations of alfentanil in study I.[2] (*D*) Alfentanil prediction error *versus* time.

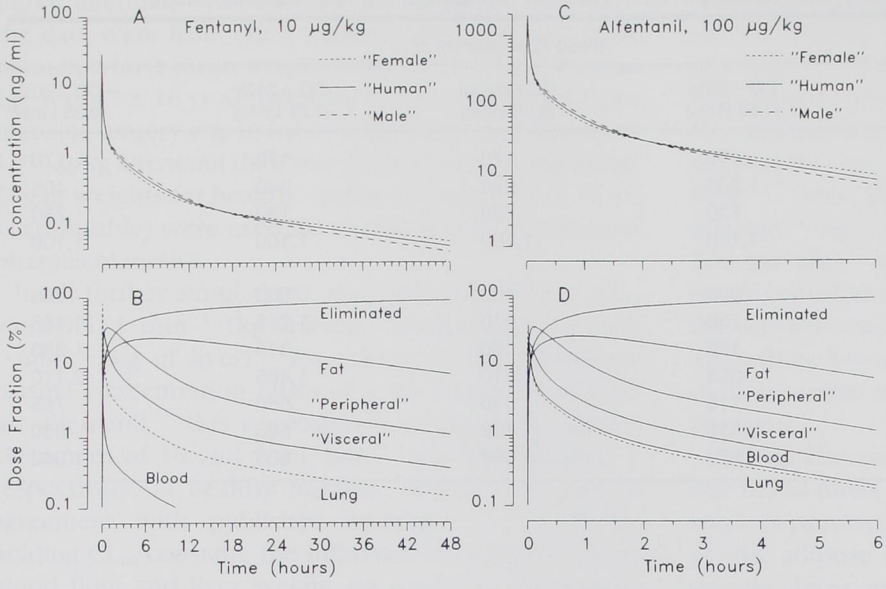

Fig. 3. (*A*) Predicted arterial plasma concentration curves of fentanyl in the "male," "female," and "human" models after administration of the indicated dose over 1 min. (*B*) The amounts of fentanyl, as a percentage of dose, eliminated or present in the large tissue compartments of the "human" model as a function of time. (*C*, *D*) The same curves for alfentanil. These plots show the relative importance of the tissue compartments for removing drug from the circulation. Compartments with similar rates of drug uptake have been grouped together: "Visceral" = brain, heart, liver, gut, pancreas, spleen, and kidneys; "peripheral" = muscle, skin, and carcass. "Blood" is great vessel blood only because the tissue compartments include capillary blood. The time scales correspond to approximately 90% elimination of either drug in the "human" model. Note the marked similarities in disposition (except for dose fractions in blood) between the two opioids after shifting of the time scale.

not shown) were obtained for alfentanil study II, with a prediction error of −0.4 ± 44%. Mean prediction errors per participant varied from −15% to 13%. In both alfentanil studies, the scatter of residuals increased with time but still encompassed the zero line.

Figure 3 shows predicted arterial plasma concentration curves of the opioids in a healthy man, woman, or "human." With weight-adjusted dosing, the early parts of the curves virtually overlapped. The peak plasma concentrations of fentanyl differed by <6% and those of alfentanil by <8%. Further results thus will be given only for simulations in "humans." As a result of pulmonary uptake and release of fentanyl, maximal concentration (30 ng/ml) in the arterial blood appeared 13 s after the end of the injection. In the first passage through the systemic circulation, 80% of the fentanyl was extracted by the organs and tissues (69% by distribution and 11% by hepatic elimination), whereas 20% was shunted directly to the central veins. The maximal central venous blood concentration was then 8.5 ng/ml 49 s after the end of injection. For alfentanil, due to lower pulmonary uptake, maximal arterial concentration (1,847 ng/ml) appeared at the end of the injection. In the first pass through the systemic circulation, 54% was extracted by distribution, 8% was eliminated, and 38% was shunted. The peak central venous plasma concentration was then 869 ng/ml 25 s after the end of injection.

Figure 3 also shows the predicted tissue disposition of the opioids. The amount of fentanyl in the lungs peaked at 85% of the dose at the end of the injection. In addition, 4.6% of fentanyl resided in great vessel blood. Maximal amounts were then 33% of the dose in the "visceral" compartments at 10 min and 39% in the "peripheral" compartments at 45 min. The peak concentration in fat was not reached until 7.4 h after the injection, but at this time the fat compartment held 27% of the injected dose, or 64% of the amount of fentanyl remaining in the body. The observed terminal half-life of fentanyl is determined by the release of fentanyl from this compartment and by the hepatic clearance. The terminal half-life was 21 h in the "human," 19 h in the "male," and 23 h in the "female" models. These long half-lives only became apparent approximately 24 h after the injection. When a three-compartment model was fitted to 21 data points "sampled" from the simulated curves in "humans" at 0–24 h, the apparent "terminal" half-life became 8.1 h and the V_{dss} became 4.6 l/kg.

The peak amount of alfentanil in the lungs was 39% of the dose. The fraction of the dose present in great vessel blood was considerably greater than for fentanyl (compare fig. 3B): 25% at the end of injection and still 0.2% at 6 h. At 52 min, the fat compartment held 57% of the remaining amount of alfentanil in the body. Because compartmental equilibration of alfentanil is rapid, terminal half-lives of 2.3 h in "humans," 2 h in "males," and 2.6 h in "females" were apparent as early as 2 h after the injection.

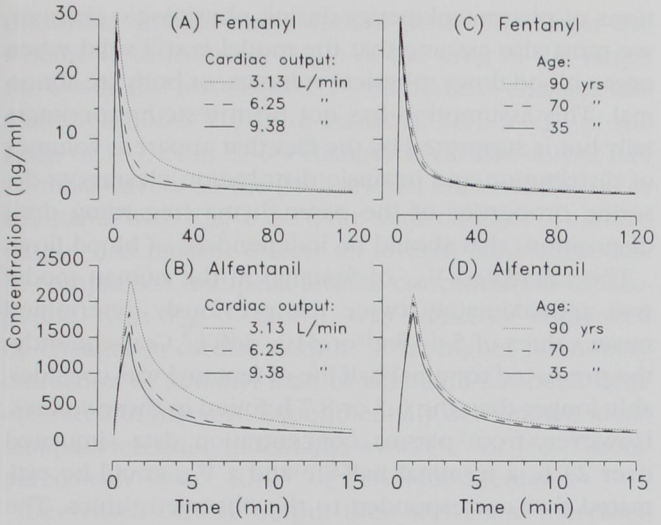

Fig. 4. Predicted arterial plasma concentration curves of (*A*) fentanyl and (*B*) alfentanil in humans with a stable cardiac output of 3.13, 6.25, or 9.38 l/min. The maximal effect of the low cardiac output was a 103% increase in fentanyl concentration at 18 min and of the high cardiac output a decrease by 36% at 9 min, as compared with the normal situation. The low cardiac output led to an increase of alfentanil concentration by 77% at 5 min and the high cardiac output to a decrease by 22% at 3 min. (*C*, *D*) Predicted arterial plasma concentration curves of the opioids in humans who were 35, 70, and 90 yr old. As in figure 3, fentanyl concentrations are depicted over a time scale that is eight times longer than that for alfentanil concentrations.

Dependence of the early disposition of the opioids on cardiac output in a young adult is shown in figures 4A and 4B. Maximal arterial concentration of fentanyl was largely unaffected, whereas that of alfentanil was increased by 24% at 3.13 l/min and decreased by 15% at 9.38 l/min. At 13 min, the overall difference in arterial plasma concentration was maximal for fentanyl. At this time, with cardiac output at 3.13 l/min, 66% of the dose was still in the lungs and "visceral" compartments and 24% had been redistributed to "peripheral" compartments and fat. With cardiac output at 9.38 l/min, only 33% of the dose was in the lungs and "viscera" and 53% had been redistributed. Corresponding numbers for alfentanil at the time of greatest difference in arterial concentrations (4.3 min) were 39% in lungs and "viscera" and 31% in "peripheral" compartments and fat at the low cardiac output, changing to 24% and 53% at the high cardiac output. Plasma clearance also decreased with a lowered cardiac output (and thus lower Q_{hep}), from 0.77 l/min at a cardiac output of 9.38 l/min to 0.47 l/min at a cardiac output of 3.13 l/min for fentanyl and from 0.37 l/min to 0.25 l/min for alfentanil. This had little influence on early disposition, however. The fraction of the fentanyl dose eliminated at 120 min was 34–36% in all three cases, and for alfentanil at 15 min the eliminated fractions were 30–33%.

Figures 4C and D show the predicted effects of age-related physiologic changes on the disposition of the opioids. For fentanyl, the difference in peak concentration between the 35-yr-old and the 90-yr-old was <1 ng/ml (3%). The greatest differences occurred approximately 10 min after the injection, which coincides with (impaired) drug distribution to "visceral" and "peripheral" compartments (see fig. 3). Diminishing clearance with age, from 0.67 l/min at 35 yr to 0.53 l/min at 70 yr and 0.40 l/min at 90 yr, combined with increasing mass of adipose tissue, then prolongs the terminal half-life from 21 h to 29 h at 70 yr and 37 h at 90 yr. For alfentanil, there was a modest increase in peak plasma concentration with age, by 8% in the septua- and 14% in the nonagenarian compared with young adults. As with fentanyl, however, the differences became greater at the time when distribution to "visceral" and "peripheral" compartments is of importance to remove drug from the circulation. Total plasma clearance diminished from 0.33 to 0.27 and 0.21 l/min and terminal half-life was prolonged from 2.3 to 3.1 and 4.0 h, respectively, in those aged 70 and 90 yr.

Figures 5A and 5B show the effects of fluctuations in various blood flows on arterial plasma concentrations of the opioids. The effects are quite small, with the most marked variation for both fentanyl and alfentanil within ±12% of the concentration during stable hemodynamics. Fluctuations every 15, 30, or 120 min gave similar patterns, with the amplitude of the changes in arterial concentrations increasing slightly with longer periods.

Figures 5C and 5D show the effects of sudden "postoperative" increases in cardiac output on arterial plasma concentration curves of fentanyl and alfentanil. At a very early time after the bolus injection of fentanyl, the large tissues such as muscle and fat are still taking up drug (see fig. 3), and increases in regional blood flows enhance this uptake, giving an extra decrease in plasma concentration. Elimination of drug is also enhanced, by the increase in hepatosplanchnic blood flow. In all other cases shown, the increased elimination is combined with enhanced release of drug from the tissue compartments, resulting in a secondary peak in arterial drug concentration followed by a decline with a shorter half-life. The secondary peaks were fractionally smaller with alfentanil than with fentanyl.

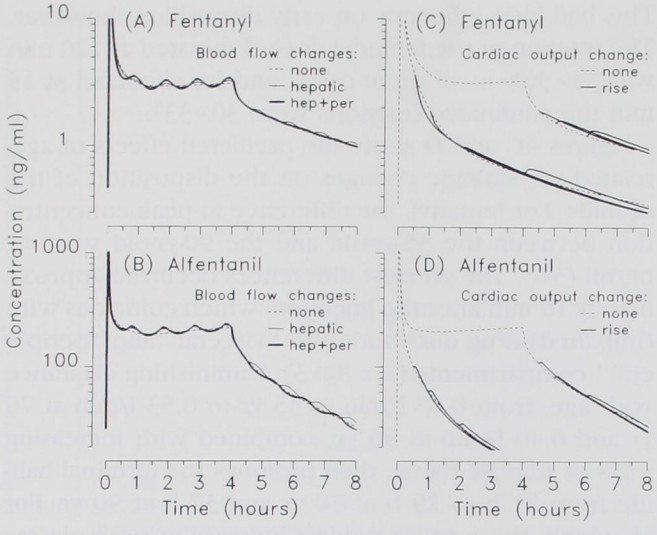

Fig. 5. (*A*, *B*) Predicted arterial plasma concentration curves of 10 μg/kg fentanyl injected over 1 min and 0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$ as a maintenance infusion, and of 100 μg/kg alfentanil and 1.2 $\mu g \cdot kg^{-1} min^{-1}$ as the maintenance infusion. Simulated changes in blood flows are "none" = stable hemodynamic conditions, "hepatic" = ±50% fluctuations in total hepatic blood flow in 1-h cycles, and "hep[atic] + per[ipheral]" = ±50% fluctuations in total hepatic and peripheral blood flows with the cardiac output changing by ±34%. (*C*, *D*) Predicted arterial plasma concentration curves of fentanyl and alfentanil. Simulated changes in cardiac output are "none" = stable hemodynamic conditions and "rise" = a "postoperative" increase in cardiac output from 4.7 to 7.8 l/min at various times after the injection or end of the infusion.

Discussion

The inherent assumptions in scaling physiologic models from rats to humans are that apparent volumes of distribution and intrinsic distribution clearances of the drug, both scaled to organ mass, are equal in the two species and that human organ volumes and blood flows can be estimated as needed from the physiologic literature.[22] The general agreement between predicted and measured plasma concentrations of the opioids support these assumptions. All available information about the patients was incorporated into the modeling. Further refinement of the predictions to give even better agreement with measured concentrations therefore would not be feasible, except by arbitrary manipulation of input data. For instance, the prolonged secondary increase in the measured concentrations in fentanyl study I, starting at 5 h, which was not predicted by the model, could be due to circulatory changes at termination of surgery and during postoperative intensive care that were not incorporated into the simulations. For predictions of pharmacokinetics during physiologic changes, we must also assume that the model is still valid when organ blood flows, physical volumes, or both are abnormal. This assumption has not been tested experimentally but is supported by the fact that apparent volumes of distribution and intrinsic distribution clearances describe properties of the parenchyma (regarding drug disposition) that should be independent of blood flow.

The calculated V_{dss} of fentanyl in the human model was approximately twice the previously determined mean values of 5.4 l/kg[3] or 310–340 l.[5] Consequently, the predicted terminal half-life of fentanyl was considerably longer than the 6.5 or 8.7 h found in these studies. However, from plasma concentration data simulated over 24 h, a terminal half-life and a V_{dss} could be estimated that corresponded to the observed values. The simulations thus suggest that the true V_{dss} and terminal half-life of fentanyl will be underestimated in studies with 24 h of blood sampling. The resulting underestimation of area under the curve and consequent overestimation of CL_{hep}, especially with even shorter sampling times,[29] justifies our decision to reduce clearance from the published values in the model verifications. The pharmacokinetics of fentanyl have been studied in critically ill patients who received infusions over several days, thus allowing distribution equilibrium to be attained in all tissues.[21,37] In 19 children, V_{dss} values of 5.1–30.5 l/kg and terminal half-lives of 11–36 h[21] were found, and in one adult patient a V_{dss} of 14 l/kg and a terminal half-life of 13 h were observed.[37] Further studies with long sampling protocols therefore may confirm the predictions of the model. The calculated V_{dss} and predicted half-life of alfentanil correspond closely with published findings.[2,8–10,20,30]

The influence of sex on the pharmacokinetics of alfentanil has been investigated to a limited extent.[4,7,9] Generally, no differences have been observed,[4,7] even though clearance was found to be inversely related to age in women but not in men.[9] Our simulations confirm that no important influence should be found. The predicted small differences in V_{dss} and half-lives presumably would not stand out from normal human inter-individual variations.

During injection, drugs are diluted into a circulating volume of venous blood that is directly proportional to cardiac output. Thus a higher cardiac output gives a lower pulmonary artery concentration curve.[38] The concentration profile is then further modified by distribution in the lungs. Only a fraction of the dose of a lipophilic opioid will be shunted through the lungs to give

the initial arterial concentration peak. The larger the volume of distribution (V_{app}) of the drug in the lungs, the lower and less affected by blood flow changes this fraction will be. Thus, for fentanyl, with a V_{app} in the lungs of 18 l, even ±50% changes in cardiac output had minimal effects on the peak arterial concentration. For alfentanil, with V_{app} = 2.2 l, the same changes in cardiac output had modest effects on arterial concentrations. In comparison, the peak arterial concentration of thiopental, with V_{app} = 0.68 l, was markedly influenced by changes in cardiac output.[22] The higher pulmonary extraction of fentanyl than of alfentanil has been demonstrated in humans. Experimentally determined mean first-pass retention of fentanyl was 71%[27] or 75%,[39] compared with 59%,[27] 10%,[40] or 20%[41] for alfentanil.

Decreased cardiac output then slows and increased cardiac output quickens drug redistribution. Thus, a higher cardiac output decreases the time when drug is in transit through the circulation, and the early decay of the arterial plasma concentration curve becomes more rapid. This has been observed experimentally as a positive correlation of total intercompartmental clearance of alfentanil (*i.e.*, distribution from the circulation to tissue compartments) with cardiac output in healthy volunteers.[11] This study also showed that total intercompartmental clearance was less than the cardiac output, suggesting that some alfentanil is always shunted directly from the arterial to the venous circulation without being distributed to tissue parenchyma, a phenomenon that was first observed with inulin and gallamine as model substances.[42] Our simulations, as well as observations in the underlying animal studies,[24,25] confirm that such shunting occurs also with the lipophilic opioids.

Several studies[1-10] address the effects of age on the pharmacokinetics of the opioids. However, there is no clear reason why the age of a patient should influence the pharmacokinetics of a drug. Rather age must be viewed as a substitute parameter that may correlate, often poorly, with physiologic changes that can actually influence drug disposition.

Two studies of fentanyl[1,6] report approximately 1.5-fold higher early arterial plasma concentrations per injected dose in elderly compared with young adults, which is more than predicted by our simulations. However, fentanyl was given immediately after induction of anesthesia with thiopental. Because elderly patients are more sensitive than young ones to the circulatory effects of thiopental,[43] this may have exaggerated the concentration differences attributed to aging. Other pharmacokinetic parameters estimated in these studies are unreliable because of short blood sampling times. In technically more satisfactory studies,[3,5] no correlations were found between pharmacokinetic values and age in men aged 55-80 yr[3] or 20-88 yr.[5]

Reported findings on the effects of aging on the pharmacokinetics of alfentanil are far from consistent. In some studies, primarily[2,4] or only[9] on women, the difference in clearance between elderly (approximately 70 yr) and young adults was variably reported as a decrease of approximately 30%,[2] 20%,[4] or 50%.[9] Other studies, including all wholly[5,9] or primarily[10] in men but also one[8] mainly in women, failed to find age-related changes in clearance. A prolonged terminal half-life in the elderly is normally[2,4,5,8-10] found (in addition, an almost 10-fold difference in clearance as well as in terminal half-life between young and elderly patients having surgery has been reported,[7] but the values given are implausible).

Our simulations predict that age-related changes in physiologic state will have only a minor influence on the pharmacokinetics of fentanyl and alfentanil in elderly (aged approximately 70 yr) persons, but such influences may become more pronounced in the very old. In the four cited studies on fentanyl,[1,3,5,6] only two patients[5] can be identified as being aged at least 80 yr. In the six studies on alfentanil that give original data,[2,5,7-10] only 10 patients[2,5,8] of 152 were 80 yr or older. Together with sex-related[9] differences not previously accounted for, this may explain why influences of aging are not consistently observed in clinical pharmacokinetic studies. Still, age-related changes in physiologic composition appear to have little effect on the clinically important early disposition of the opioids.

The selected perturbations of blood flows were based on physiologic findings in humans. Cerebral blood flow is subject to autoregulation and therefore was never changed. Muscle blood flows used in our simulations are compatible to values measured in going from complete rest to modest exercise,[34,35] and skin blood flow was varied in parallel with muscle blood flow.[34,36] High-resolution measurements of cardiac output in patients during general anesthesia[13,14] have shown that fluctuations by 1-3 l/min can occur within minutes, seemingly randomly[13] or as a response to identifiable surgical stress.[14] The clinical causes of per- or postoperative increases in cardiac output and peripheral blood flows may include resumption of normal muscle activity after reversal of neuromuscular blockade, onset of postoperative pain, or physiologic changes caused by mechanical ventilation or the surgery itself.

During infusions of opioids, fluctuations of measured concentrations around the predicted smooth concentration curves are always seen.[37,44,45] These are expressed as a prediction error of at least 20%,[44,45] based on the use of a conventional mamillary model. The fluctuations can, in part, be explained by changes in blood flows (figs. 5A and 5B). However, additional unexplained error, due, for example, to assay, sampling, ventilatory fluctuations, and blood volume shifts, must remain.

Secondary increases in plasma concentration of fentanyl are often observed[1,3,15-18,20,21] (see fig. 2). They generally appear on recovery from anesthesia,[1,3,15] although they may be seen also during surgery[1] (as in figs. 5A and 5B) and in nonanesthetized volunteers.[17,18] Secondary peaks of alfentanil have been observed,[10,19] but this is unusual. Our simulations support release from peripheral tissues, chiefly muscle,[17,20,21] as a probable mechanism. Identical changes in blood flows in the physiologic model produced smaller secondary peaks of alfentanil than of fentanyl, which confirms that release of pharmacologically important amounts of alfentanil from tissue stores is unlikely to occur.

In conclusion, the physiologic pharmacokinetic models were able to predict plasma concentrations of fentanyl or alfentanil after short infusions in patients having surgery. The disposition of the opioids appeared to be only modestly influenced by changes in physiologic state. Compensatory dose adjustments, as earlier suggested for thiopental,[22] do not seem generally warranted. However, adjusting the dose of opioid for cardiac output (or for age and fitness of the patient, as substitute parameters) should help to normalize time of recovery from the opioid effects. Changes in clearance, V_{dss}, and terminal half-life with cardiac output (or age) are of minor consequence for recovery from the effects of a single dose of opioid, but they may become important with repeated or continuous administration. Fluctuations in cardiac output and peripheral blood flows during or after the administration of the opioids seem to have little net effect on their disposition. Thus the common use of these opioids in critically ill and hemodynamically unstable patients is rational.

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References

1. Bentley JB, Borel JD, Nenad RE, Gillespie TJ: Age and fentanyl pharmacokinetics. Anesth Analg 1982; 61:968-71

2. Helmers H, Van Peer A, Woestenborghs R, Noorduin H, Heykants J: Alfentanil kinetics in the elderly. Clin Pharmacol Ther 1984; 36:239-43

3. Hudson RJ, Thomson IR, Cannon JE, Friesen RM, Meatherall RC: Pharmacokinetics of fentanyl in patients undergoing abdominal aortic surgery. ANESTHESIOLOGY 1986; 64:334-8

4. Maitre PO, Vozeh S, Heykants J, Thomson DA, Stanski DR: Population pharmacokinetics of alfentanil: The average dose-plasma concentration relationship and interindividual variability in patients. ANESTHESIOLOGY 1987; 66:3-12

5. Scott JC, Stanski DR: Decreased fentanyl and alfentanil dose requirements with age. A simultaneous pharmacokinetic and pharmacodynamic evaluation. J Pharmacol Exp Ther 1987; 240:159-66

6. Singleton MA, Rosen JI, Fisher DM: Pharmacokinetics of fentanyl in the elderly. Br J Anaesth 1988; 60:619-22

7. Sitar DS, Duke PC, Benthuysen JL, Sanford TJ, Smith NT: Aging and alfentanil disposition in healthy volunteers and surgical patients. Can J Anesth 1989; 36:149-54

8. Van Beem H, Van Peer A, Gasparini R, Woestenborghs R, Heykants J, Noorduin H, Van Egmond J, Crul J: Pharmacokinetics of alfentanil during and after a fixed rate infusion. Br J Anaesth 1989; 62:610-5

9. Lemmens HJM, Burm AGL, Hennis PJ, Gladines MPPR, Bovill JG: Influence of age on the pharmacokinetics of alfentanil: Gender dependence. Clin Pharmacokinet 1990; 19:416-22

10. Hudson RJ, Thomson IR, Burgess PM, Rosenbloom M: Alfentanil pharmacokinetics in patients undergoing abdominal aortic surgery. Can J Anaesth 1991; 38:61-7

11. Henthorn TK, Krejcie TC, Avram MJ: The relationship between alfentanil distribution kinetics and cardiac output. Clin Pharmacol Ther 1992; 52:190-6

12. Gelman S, Frenette L: Effects of anaesthetics on liver blood flow. Baillières Clin Anaesthesiol 1992; 6:729-50

13. Doi M, Morita K, Ikeda K: Frequently repeated Fick cardiac output measurements during anesthesia. J Clin Monit 1990; 6: 107-12

14. Rieke H, Weyland A, Hoeft A, Weyland W, Sonntag H, Breme S: Kontinuierliche HZV-Messung nach dem Fickschen Prinzip in der Kardioanaesthesie. Anaesthesist 1990; 39:13-21

15. McQuay HJ, Moore RA, Paterson GMC, Adams AP: Plasma fentanyl concentrations and clinical observations during and after operation. Br J Anaesth 1979; 51:543-50

16. Stoeckel H, Hengstmann JH, Schüttler J: Pharmacokinetics of fentanyl as a possible explanation for recurrence of respiratory depression. Br J Anaesth 1979; 51:741-5

17. McClain DA, Hug CC: Intravenous fentanyl kinetics. Clin Pharmacol Ther 1980; 28:106-14

18. Stoeckel H, Schüttler J, Magnussen H, Hengstmann JH: Plasma fentanyl concentrations and the occurrence of respiratory depression in volunteers. Br J Anaesth 1982; 54:1087-95

19. Camu F, Gepts E, Rucquoi M, Heykants J: Pharmacokinetics of alfentanil in man. Anesth Analg 1982; 61:657-61

20. Mather LE: Clinical pharmacokinetics of fentanyl and its newer derivatives. Clin Pharmacokinet 1983; 8:422-46

21. Katz R, Kelly HW: Pharmacokinetics of continuous infusions of fentanyl in critically ill children. Crit Care Med 1993; 21:995-1000

22. Wada DR, Björkman S, Ebling WF, Harashima H, Harapat SR, Stanski DR: Computer simulation of the effects of alterations in blood flows and body composition on thiopental pharmacokinetics in humans. ANESTHESIOLOGY 1997; 87:884-99

23. Björkman S, Stanski DR, Verotta D, Harashima H: Comparative tissue concentration profiles of fentanyl and alfentanil in humans predicted from tissue/blood partition data obtained in rats. ANESTHESIOLOGY 1990; 72:865–73

24. Björkman S, Stanski DR, Harashima H, Dowrie R, Harapat SR, Wada DR, Ebling WF: Tissue distribution of fentanyl and alfentanil in the rat cannot be described by a blood flow limited model. J Pharmacokin Biopharm 1993; 21:255–79

25. Björkman S, Wada DR, Stanski DR, Ebling WF: Comparative physiological pharmacokinetics of fentanyl and alfentanil in rats and humans based on parametric single-tissue models. J Pharmacokin Biopharm 1994; 22:381–410

26. Wada DR, Ward DS: The hybrid model: A pharmacokinetic model for computer-controlled infusion pumps. IEEE Trans Biomed Eng 1994; 41:134–42

27. Taeger K, Weninger E, Schmelzer F, Adt M, Franke N, Peter K: Pulmonary kinetics of fentanyl and alfentanil in surgical patients. Br J Anaesth 1988; 61:425–34

28. Williams LR, Leggett RW: Reference values for resting blood flow to organs of man. Clin Phys Physiol Meas 1989; 10:187–217

29. Varvel JR, Shafer SL, Hwang SS, Coen PA, Stanski DR: Absorption characteristics of transdermally administered fentanyl. ANESTHESIOLOGY 1989; 70:928–34

30. Bovill JG, Sebel PS, Blackburn CL, Heykants J: The pharmacokinetics of alfentanil (R39209): A new opioid analgesic. ANESTHESIOLOGY 1982; 57:439–43

31. Meuldermans WEG, Hurkmans RMA, Heykants JJP: Plasma protein binding and distribution of fentanyl, sufentanil, alfentanil and lofentanil in blood. Arch int Pharmacodyn 1982; 257:4–19

32. Stenson RE, Constantino RT, Harrison DC: Interrelationships of hepatic blood flow, cardiac output, and blood levels of lidocaine in man. Circulation 1971; 43:205–11

33. Rosell S, Belfrage E: Blood circulation in adipose tissue. Physiol Reviews 1979; 59:1078–104

34. Kontos HA, Richardson DW, Patterson JL: Blood flow and metabolism of forearm muscle in man at rest and during sustained contraction. Am J Physiol 1966; 211:869–76

35. Grimby G, Häggendal E, Saltin B: Local xenon 133 clearance from the quadriceps muscle during exercise in man. J Appl Physiol 1967; 22:305–10

36. Edholm OG, Fox RH, Macpherson RK: The effect of body heating on the circulation in skin and muscle. J Physiol 1956; 134:612–9

37. Shafer A, White PF, Schüttler J, Rosenthal MH: Use of a fentanyl infusion in the intensive care unit: Tolerance to its anesthetic effects? ANESTHESIOLOGY 1983; 59:245–8

38. Upton RN, Huang YF: Influence of cardiac output, injection time and injection volume on the initial mixing of drugs with venous blood after i.v. bolus administration to sheep. Br J Anaesth 1993; 70:333–8

39. Roerig DL, Kotrly KJ, Vucins EJ, Ahlf SB, Dawson CA, Kampine JP: First pass uptake of fentanyl, meperidine, and morphine in the human lung. ANESTHESIOLOGY 1987; 67:466–72

40. Boer F, Bovill JG, Burm AGL, Mooren RAG: Uptake of sufentanil, alfentanil and morphine in the lungs of patients about to undergo coronary artery surgery. Br J Anaesth 1992; 68:370–5

41. Boer F, Bovill JG, Burm AGL, Hak A: Effect of ventilation on first-pass pulmonary retention of alfentanil and sufentanil in patients undergoing coronary artery surgery. Br J Anaesth 1994; 73:458–63

42. Henthorn TK, Avram MJ, Frederiksen MC, Atkinson AJ: Heterogeneity of interstitial fluid space demonstrated by simultaneous kinetic analysis of the distribution and elimination of inulin and gallamine. J Pharmacol Exp Ther 1982; 222:389–94

43. Christensen JH, Andreasen F, Jansen JA: Pharmacokinetics and pharmacodynamics of thiopentone. A comparison between young and elderly patients. Anaesthesia 1982; 37:398–404

44. Maitre PO, Ausems ME, Vozeh S, Stanski DR: Evaluating the accuracy of using population pharmacokinetic data to predict plasma concentrations of alfentanil. ANESTHESIOLOGY 1988; 68:59–67

45. Shafer SL, Varvel JR, Aziz N, Scott JC: Pharmacokinetics of fentanyl administered by computer-controlled infusion pump. ANESTHESIOLOGY 1990; 73:1091–102