Accuracy of Pharmacokinetic Models for Predicting Plasma Fentanyl Concentrations in Lean and Obese Surgical Patients

Derivation of Dosing Weight ("Pharmacokinetic Mass")

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Background: The currently available pharmacokinetic models for fentanyl were derived from normal weight patients and were not scaled to body weight. Their application to obese patients may cause overprediction of the plasma concentration of fentanyl. This study examined the influence of body weight on the predictive accuracy of two models (ANESTHESIOLOGY 1990; 73:1091–102 and J Pharmacol Exp Ther 1987; 240:159–66). Further, we attempted to derive suggested dosing mass weights for fentanyl that improved predicted accuracy.

Method: Seventy patients undergoing major elective surgery with total body weight (TBW) <85 kg and body mass index <30 (Group L) and 39 patients with TBW ≥85 kg and body mass index >30 (Group O) were studied. In Group L and Group O, the mean TBW was 69 kg, and 125 kg, respectively and the mean body mass index in Group L and Group O was 24 and 44, respectively. Fentanyl infusion was used during surgery and postoperatively for analgesia. Plasma fentanyl concentrations were measured and predicted concentrations were obtained by computer simulation; 465 pairs of measured and predicted values were obtained.

Results: The influence of TBW on the performance errors of the original two models was examined with nonlinear regression analysis. Shafer error *versus* TBW showed a highly significant negative relationship (R squared = 0.689, P < 0.001); *i.e.*, the Shafer model systematically overestimated fentanyl concentration as weight increased. The Scott and Stanski model showed greater variation (R squared = 0.303). We used the exponential equation for Shafer performance error *versus* TBW to derive suggested dosing weights ("pharmacokinetic mass") for obese patients. The pharmacokinetic mass *versus* TBW curve was essentially linear below 100 kg (with slope of 0.65) and approached a plateau above 140 kg. For patients weighing 140 to 200 kg, dosing weights of 100–108 kg are projected. Total body clearance (ml/min) showed a strong linear correlation with pharmacokinetic mass (r = 0.793; P < 0.001), whereas the relationship with TBW was nonlinear.

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Conclusion: Actual body weight overestimates fentanyl dose requirements in obese patients. Dosing weight (pharmacokinetic mass) derived from the nonlinear relationship between prediction error and TBW proved to have a linear relationship with clearance.

THREE-compartment pharmacokinetic models have been used to predict plasma fentanyl concentrations and have been implemented in clinical practice as target-controlled infusion.[1–3] The pharmacokinetic parameters used in the currently available pharmacokinetic programs, such as the Shafer model[1] and the Scott and Stanski model,[4] are not scaled to body weight. Shafer *et al.*[1] attempted to scale pharmacokinetic parameters of their model to weight, but improvement of the prediction was not observed as compared to the non–weight-scaled program. Therefore they chose the unscaled parameters as the simple model and suggested that these pharmacokinetic parameters only be used in target-controlled infusions or simulations for patients whose body weights are within 1 SD of the mean weight. The mean body weight and SD of the patients included in the study by Shafer *et al.*[1] were 69 ± 17 kg.

Although opioid dosage regimens are often based on total body weight (TBW) and many package inserts explicitly provide per kilogram dosing, the influence of body weight on the pharmacokinetics of fentanyl has not been established.[5] In morbidly obese patients, in addition to the increased TBW, there is an increased proportion of body fat to total body mass. Furthermore, both cardiac output and intravascular volume are increased.[6] Therefore, it is not known whether the pharmacokinetic model that is not scaled to body weight can predict plasma fentanyl concentrations in obese patients as well as in normal weight patients.

The purpose of this study was to examine the influence of TBW and other indices of body mass on the accuracy of predicting plasma fentanyl concentrations in lean and obese patients. The Shafer model and the Scott and Stanski model were used to quantify the extent of departure from linearity of the relationship between fentanyl pharmacokinetics and body weight as body weight increases. We have used the extent of departure from linearity to attempt to derive suggested dosing weights for fentanyl over the broad range of lean and obese patients. We have termed these dosing weights "pharmacokinetic mass." Total body clearance values

were also determined and their relationship was compared to TBW and pharmacokinetic mass.

Materials and Methods

Seventy patients undergoing major elective surgery with body mass index (BMI) less than 30 and weighing less than 85 kg (Group L) and 39 patients with BMI greater than 30 and weighing equal to or more than 85 kg (Group O) were studied after the approval of the Institutional Review Board of New York Medical College, Valhalla, New York. Informed consent was waived by the institutional review board because the study was performed using residual blood discarded from blood gas analyses in patients that would routinely require arterial cannulation for monitoring and blood gas analysis. The pharmacokinetic simulations were not used to guide therapy, in fact, they were carried out after the cases were completed. The types of surgery included abdominal aortic aneurysmectomy, major abdominal surgery, open abdominal gastric bypass surgery, and surgery for scoliosis with spinal instrumentation. Patients with liver or renal disease and those requiring chronic analgesic medication were not included in the study. Patients with cardiac disease, chronic obstructive pulmonary disease, or morbid obesity were not excluded.

Anesthesia was induced with fentanyl 1–2 μg/kg, propofol 1.5 to 2.5 mg/kg, sevoflurane 2% and atracurium 0.5 mg/kg. After the initial bolus dose of fentanyl, a continuous infusion of fentanyl was started at the rate of 0.05–0.07 μg·kg^{-1}·min^{-1} for 60 to 75 min, followed by an infusion rate of 0.03–0.05 μg·kg^{-1}·min^{-1} for 1 to 2 h, and then the infusion rate was reduced to 0.02–0.03 μg·kg^{-1}·min^{-1}. The exact infusion rate of fentanyl, however, was adjusted by the participating anesthesiologists to meet the clinical need in each case. The infusion of fentanyl was discontinued approximately 30–40 min before the estimated end of surgery. Extubation was expected in the operating room unless severe hemodynamic instability was present. After arrival in the postanesthesia care unit or postoperative care unit a continuous fentanyl infusion was resumed for analgesia at a rate of 0.5–2.0 μg·kg^{-1}·h^{-1}. However, the infusion rates were adjusted in each case according to analgesic effectiveness of the fentanyl infusion, the respiratory rate, and the state of consciousness of the patients. In patients who stayed in the postoperative care unit, the fentanyl infusion was continued to the next morning. In patients who stayed in the postanesthesia care unit, the infusion of fentanyl was discontinued when the patients were discharged after 4 to 8 h in the unit. Arterial blood samples for blood gas analysis were obtained during the first 2 h of surgery (Stage 1),

during the latter part of surgery (Stage 2), at the end of surgery or during the early postoperative period (Stage 3), and during the late postoperative period of the day or on the next morning (Stage 4). The residuals of arterial blood samples that were drawn for blood gas analyses were allowed to partially clot and were centrifuged within 2 h; plasma (serum) was stored at $-70°C$ until radioimmunoassay for fentanyl concentration. Radioimmunoassays were performed at the Department of Anatomy, Physiologic Sciences and Radiology of North Carolina State University, Raleigh, North Carolina. The assay had a lower limit of quantification of 0.1 ng/ml. The coefficient of variation between paired aliquots was 8.42% at 0.25 ng/ml.

The pharmacokinetic models described by Shafer *et al.*[1] and Scott and Stanski[4] were used to predict plasma concentrations of fentanyl. In conjunction with the dosing schedules for each patient, the STANPUMP program‖ was used to generate predicted plasma fentanyl concentrations for both the Shafer model (Cp-Shafer) and the Scott and Stanski model (Cp-Scott) throughout the period of the study. Thus, sets of measured plasma concentration of fentanyl (Cpm), and Cp-Shafer and Cp-Scott, respectively, were obtained. To assess accuracy (bias and precision) of the prediction of the plasma fentanyl concentration (Cp) by the pharmacokinetic models, the following values were determined:

Percent performance error (PE %) = (Cpm − Cp)/Cp × 100, mean value and SD, median value, percent of Cp within ± 30% error; absolute performance error (APE): mean value and SD, median value.

To examine the influence of TBW on performance error of the Shafer model (PE-Shafer), nonlinear regression analysis was performed. The regression equation for the relationship between PE-Shafer and TBW was used to correct bias of the prediction in the original Shafer model, and corrected Cp values were designated as Cp-Shafer-reg.

Nonlinear regression analysis was performed similarly between PE-Scott and TBW and corrected Cp values were designated as Cp-Scott-reg.

APE of the original Shafer model, Scott and Stanski model, and the corrected values by regression analyses were also determined.

As an internal test to evaluate the application of nonlinear regression analysis for prediction and correction of PE for fentanyl dosing, we divided our entire patient population randomly into two groups of approximately equal numbers of patients. One group, represented by 250 blood samples, was designated as the "training" group; the second group, represented by 215 blood samples was the "testing" group. A nonlinear regression equation for PE *versus* TBW was determined using the training group data. This equation was then used to calculate corrected PE values for the data of the testing group, and the correction of bias was compared with the

‖ Available at http://anesthesia.stanford.edu/pkpd. Accessed February 2003.

Table 1. Demographic Data

	Age (yr)	Sex (M/F)	Height (cm)	Weight (kg)	ASA (median)	BSA (m²)	BMI (kg/m²)	LBM (kg)	IBW (kg)	Surgical Duration (min)
Group L (n = 70)	60 (16)	51/19	169 (8)	69 (8)	3.0	1.8 (0.1)	24 (2)	53 (7)	63 (8)	276 (90)
Group O (n = 39)	*47 (16)	20/19†	169 (12)	125 (33)*	3.0	2.3 (0.3)*	44 (12)*	62 (12)*	63 (12)	269 (97)

Values are mean (SD).

Group L (lean group): BMI < 30, weight < 85 kg; Group O (obese group): BMI > 30, weight ≥ 85 kg.

ASA = American Society of Anesthesiologists physical status; BMI = body mass index; BSA = body surface area; IBW = ideal body weight; LBM = lean body mass.

* $P < 0.01$ *versus* Group L; †$P < 0.05$ for sex ratio *versus* Group L.

correction that was obtained with the data for the total patient population.

Clearance values were obtained from a number of patients in both the lean and obese groups who received essentially constant infusion doses of fentanyl in the postoperative care unit. In almost all instances, the final blood samples were taken the morning after surgery and when drug was still being infused. Steady-state conditions were assumed to exist, not only by the lengths of constant infusion dosing, but also from the STANPUMP simulations that were indicating steady state conditions. Clearance (Cl) was determined by the equation: Cl (ml·kg^{-1}·min^{-1} = Infusion (μg·kg^{-1}·min^{-1})/Concentration at steady state (μg/ml). This value was multiplied by TBW to obtain total body clearance (ml/min) for each patient.

Analyses were also performed between PE-Shafer and BMI, body surface area (BSA), lean body mass (LBM), and ideal body weight, respectively. The standard formulae were used to calculate these indices, which factor for both height and weight.[5] In obese patients, the standard formula for calculating LBM produces a strange artifact. For any given height, progressive increases in body weight result in a peak value for LBM; increases in body weight beyond that peak value yield decreasing values of LBM. As suggested by Bouillon and Shafer,[5] body weights above the peak were assigned the LBM peak value for that height.

PK Analyst (MicroMath Scientific Software, Salt Lake City, Utah) was used to derive nonlinear regression equations for the relationships between PE-Shafer and TBW, PE-Scott and TBW and PE-Shafer and BMI and BSA, respectively. A biexponential model of the general form, PE = $A \cdot e^{-\alpha \cdot \text{kg(etc.)}} + B \cdot e^{-\beta \cdot \text{kg(etc.)}}$ was used to fit the data. With the exception of the equation for PE *versus* BSA, the second exponential, β, was essentially zero and was dropped from the equations.

To test the statistical significance of differences in the mean values of the demographic variables between Group L and Group O, nonparametric Mann–Whitney U tests were used. For comparisons of prediction error among different sampling stages and comparison of the prediction accuracy among the several prediction methods, analysis of variance was applied, followed by *post hoc* multiple group comparisons with the Newman-Keuls test. Chi-square test was applied to the ratios of males to females in Group L *versus* Group O, comparison of the types of surgery between the groups, and the frequencies of lean and obese patients represented in the stages at which blood was sampled. The Pearson correlation coefficient was used to characterize the relationship between linear variables; R-squared values were used to express the goodness of fit for the nonlinear regression analyses. The formula for the R squared statistic is: R squared = Σ squared observations $- \Sigma$ squared deviations/Σ squared observations. Statistical significance was considered to be $P < 0.05$.

Results

The demographic data are shown in table 1. There were no significant differences between Group L and Group O in height, American Society of Anesthesiologists physical status, ideal body weight, and duration of surgery. TBW, BSA, BMI, and LBM of Group L were: 69 ± 8 kg (mean ± SD), 1.8 ± 0.1 m², 24 ± 2 kg, and 53 ± 7 kg, respectively; the corresponding values for Group O were 125 ± 33 kg, 2.3 ± 0.3 m², 44 ± 12 kg, and 62 ± 12 kg, respectively. The differences between the groups for all of these measures were statistically significant ($P < 0.01$). The ages of Group L and Group O were 60 ± 16 yr and 47 ± 16 yr, respectively; this difference was statistically significant ($P < 0.01$). However, linear regression analysis between age and PE-Shafer did not reveal an important influence of age on PE-Shafer (r = 0.134). There was also a statistically significant difference in the ratio of males to females between Group L and Group O. However, when

Table 2. Numbers of Patients in Each Type of Surgery

	Group L (n = 70)	Group O (n = 39)
Major abdominal surgery	50	29
Major vascular surgery	31	8
Other open abdominal surgery	19	21
Major orthopedic surgery	11	3
Thoracic surgery	4	0
Coronary artery bypass surgery	1	2
Others	4	5

tested separately, there were no statistically significant differences for PE-Shafer between males and females in either Group L ($P = 0.086$) or Group O ($P = 0.923$).

Table 2 lists the types of surgery performed on the patients studied. Group L had more major vascular surgery compared with Group O. Major vascular surgery was also open abdominal surgery such as infrarenal abdominal aneurysmectomy. Thus, there was no statistically significant difference in the number of abdominal surgeries between Group L and Group O (chi-square = 0.011; $P = 0.917$). In both major vascular surgery and other abdominal surgeries, a Bookwalter multiblade retractor was in place, therefore, the disturbance of blood flow to internal organs that might result from laparotomy or by retraction was unlikely in both major abdominal vascular surgery and open abdominal surgery.

Timing of samples, number of samples, mean and SD of PE-Shafer and PE-Scott, and Cpm in each stage of sampling are listed in table 3. At Stage 4 (the late postoperative period), PE-Shafer values were more negative than in Stages 1 or 3. PE-Scott values in Stage 4 were also more negative than for Stage 1. However, these differences would be expected to have been similar in both lean and obese patients because there were no differences in the ratios of lean and obese patients at any of the stages that were sampled.

Figure 1 shows the correlation between predicted and measured concentrations of plasma fentanyl in Group L and Group O using the original Shafer model. Cp-Shafer was significantly correlated with measured concentrations. The linear regression for Group L is: y = 0.89x + 0.80; r = 0.794, $P < 0.001$. For Group O: y = 1.12x + 1.38; r = 0.866, $P < 0.001$. Visual inspection reveals that Cp-Shafer consistently overpredicted Cpm in Group O. Overprediction appeared less frequently in Group L than in Group O.

To examine the influence of TBW on PE-Shafer, nonlinear regression analysis between PE-Shafer and TBW was performed and is shown in figure 2A. The equation obtained for this relationship is as follows: PE-Shafer (%) = $196.4 \times e^{-0.025kg} - 53.66$; R squared = 0.689, $P < 0.001$.

PE-Shafer is significantly influenced by TBW. It becomes increasingly negative as TBW increases. This im-
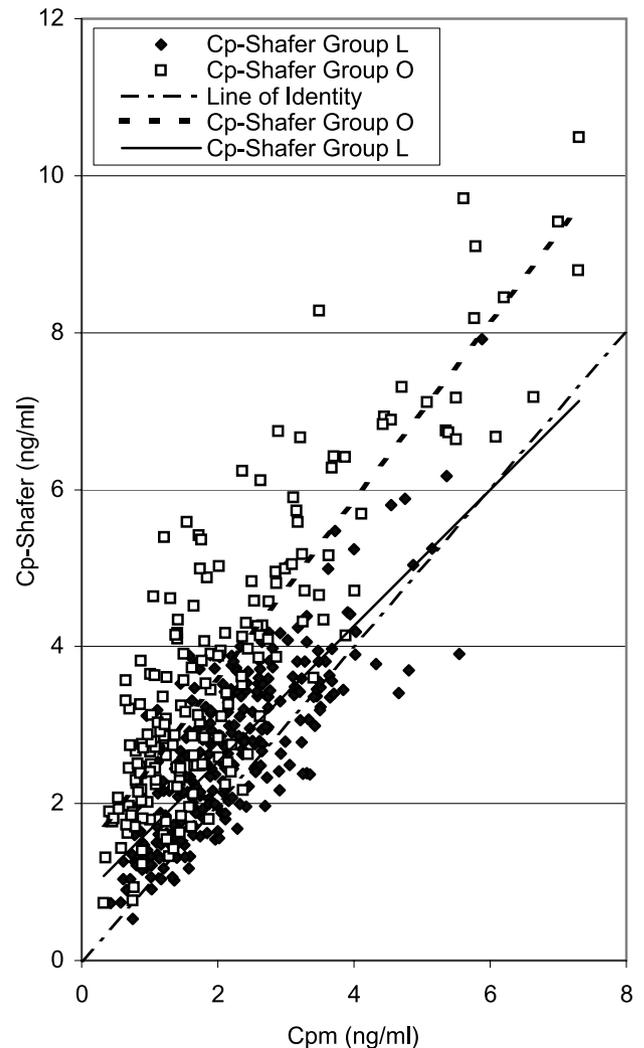

Fig. 1. The correlation between predicted and measured concentrations of plasma fentanyl in the lean group (Group L) and the obese group (Group O). The regression for Group L is: y = 0.89x + 0.80; r = 0.794, $P < 0.001$. For Group O: y = 1.12x + 1.38; r = 0.866, $P < 0.001$.

plies that Cp-Shafer systematically overestimates Cpm as TBW increases. For a patient weighing 52 kg, the mean value of PE-Shafer has no bias. For patients weighing 70, 100, 120, 140, 160, and 200 kg, mean Cpm values were

Table 3. Performance Error of the Shafer and Scott Models and Measured Plasma Fentanyl Concentrations in Each Sampling Stage

Sampling Stage	Stage 1	Stage 2	Stage 3	Stage 4
Sampling time	< 2 h	2–5 h	5–10 h	10–31 h
Number of Samples (Group L/Group O)	54/42	102/75	81/40	40/31
PE-Shafer (%)	−29 (26)*	−28 (25)	−24 (27)†	−36 (24)
PE-Scott (%)	8 (38)*	1 (33)	0 (36)	−10 (33)
Cpm (ng/ml)	2.8 (1.4)	2.4 (1.1)	1.8 (0.7)	1.6 (1.4)

Values are mean (SD).

Cpm = measured plasma fentanyl concentrations; PE-Scott = performance error of the Scott model; PE-Shafer = performance error of the Shafer model.

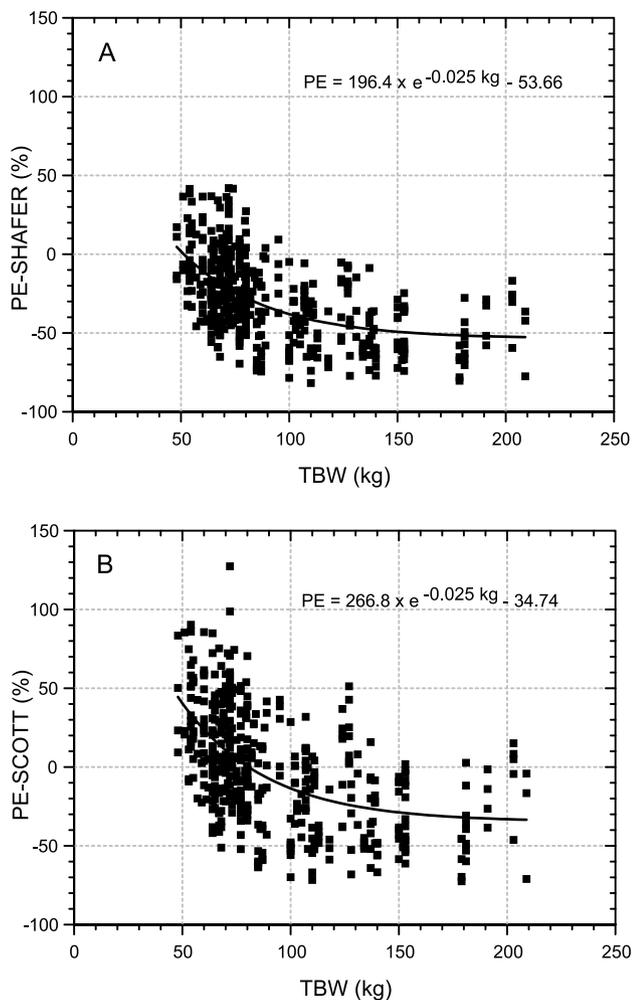* p < 0.05 *versus* Stage 4; † p < 0.05 *versus* Stage 4.

Fig. 2. (*A*) Nonlinear regression analysis between performance error with Shafer model (PE-Shafer) and total body weight (TBW). The equation for this relationship is as follows: PE(%) = 196.4 × e $^{-0.025\ kg}$ − 53.66; R squared = 0.689, *P* < 0.001. (*B*) Nonlinear regression analysis between performance error with Scott model (PE-Scott) and TBW. The equation for this relationship is: PE(%) = 266.8 × e $^{-0.025\ kg}$ − 34.74; R squared = 0.303, *P* < 0.001.

less than mean Cp-Shafer by approximately 19%, 37%, 44%, 48%, 50%, and 52%, respectively.

The formula to correct Cp-Shafer by nonlinear regression analysis between PE-Shafer and TBW is as follows: Corrected Cp (Cp-Shafer-reg) = Cp-Shafer × "correction factor;" *i.e.*, Cp-Shafer × [1 + (196.4 × e$^{-0.025kg}$ − 53.66)/100].

Nonlinear regression analysis between PE-Scott and TBW also revealed a biexponential curve (fig. 2B), similar to that of the Shafer model, with the following equation: PE-Scott (%) = 266.8 × e$^{-0.025kg}$ − 34.74; R squared = 0.303, *P* < 0.001. Corrected Cp-Scott values (Cp-Scott-reg) were calculated as for Cp-Shafer-reg, above.

There was considerably greater variation in the PE-Scott data than the PE-Shafer data. This can be seen by visual comparison of the data in figures 2A and 2B,

which are plotted on the same vertical scale. The SD for PE-Shafer was ±25.7%, compared with ±35.4% for the PE-Scott data. Therefore, we focused the remainder of our analyses primarily on the Shafer model.

The relation between TBW and correction factor is shown in figure 3A. This correction factor may be used to correct displayed plasma concentrations of STANPUMP when it is being operated in the infusion mode with the Shafer set of pharmacokinetic parameters. The relationship between Corrected Cp and Cp-Shafer can be expressed as a ratio of Cp-Shafer to Cp-Shafer-reg; thus, Cp-Shafer/Cp-Shafer-reg = 1/Correction factor. The influence of TBW on Cp-Shafer/Cp-reg-TBW is shown in figure 3B. This diagram can be used to correct the desired target plasma concentration of fentanyl to be entered in STANPUMP during target-controlled infusion. For example, to achieve a target concentration of 1 ng/ml in a patient weighing 160 kg, 2.0 ng/ml should be entered as a target concentration.

CP-Shafer overestimated Cpm as TBW increased (fig. 2A). It can be interpreted that the pharmacokinetically active body mass does not increase in proportion to TBW. If we assume that the increase of pharmacokinetic mass is proportional to overestimation of Cpm, pharmacokinetic mass may serve as a useful basis for fentanyl dosing. With this assumption, pharmacokinetic mass was calculated from the nonlinear regression analysis of the Shafer model ("pharmacokinetic mass-Shafer"). The body weight of 52 kg was used as a reference body weight to define overestimation because PE-Shafer is essentially zero at this body weight. The formula for pharmacokinetic mass-Shafer is as follows, and the relationship between pharmacokinetic mass-Shafer and TBW is shown in figure 3C: Pharmacokinetic mass-Shafer = 52/(1 + PE-Shafer-reg) = 52/Correction factor; *i.e.*, 52/[1 + (196.4 × e$^{-0.025kg}$ − 53.66)/100].

Pharmacokinetic mass-Shafer increases exponentially as TBW increases (fig. 3C). When TBW exceeds 140 kg, increases in pharmacokinetic mass appear less, implying that increases of metabolism and distribution may be small beyond this body weight.

Pharmacokinetic mass was derived similarly from the Scott and Stanski model. PE-Scott is close to zero at body weight of 82 kg. Therefore, 82 kg was used as a reference body weight in calculating pharmacokinetic mass. The formula for pharmacokinetic mass derived from the Scott-Stanski model ("pharmacokinetic mass-Scott") is as follows, and the curve in relationship to TBW is shown in fig. 3C: Pharmacokinetic mass-Scott = 82/(1 + PE-Scott-reg); *i.e.*, 82/[1 + (266.8 × e$^{-0.025kg}$ − 34.74)/100].

Pharmacokinetic mass-Shafer and pharmacokinetic mass-Scott have similar profiles and similar absolute relationships to TBW. Between body weights of 52 kg and 100 kg, both pharmacokinetic mass curves have almost identical linear slopes of approximately 0.65. When TBW exceed 140 kg, both of the pharmacokinetic mass curves flatten considerably.
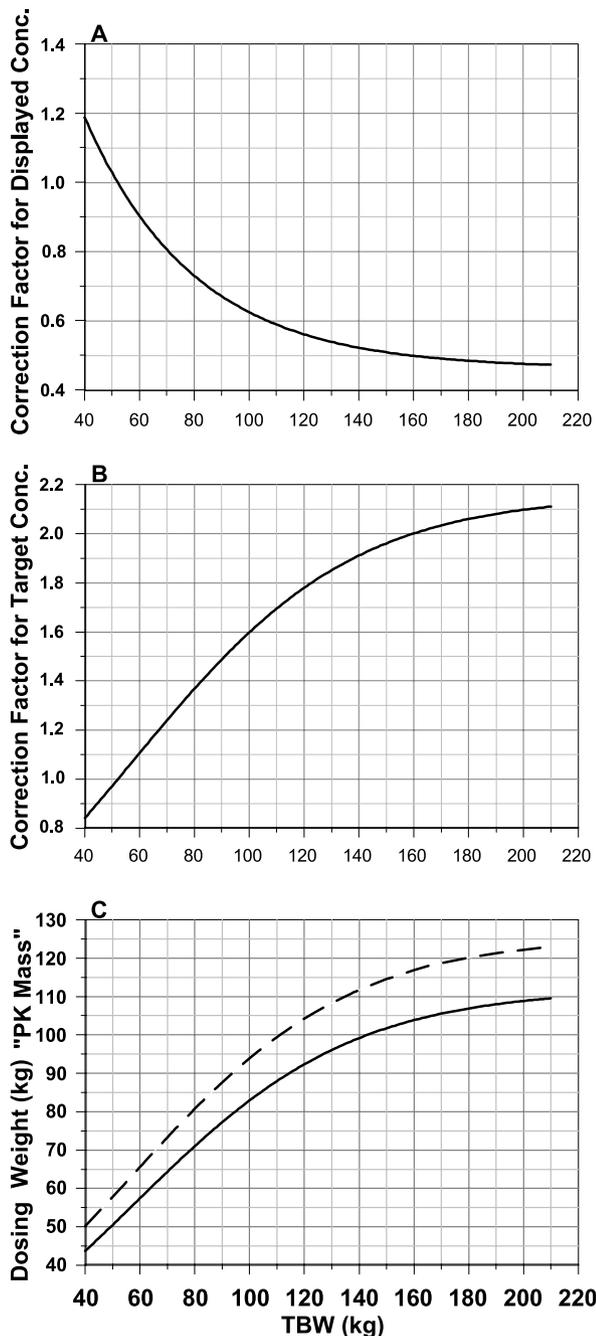
Fig. 3. (*A*) Correction factors derived from the nonlinear regression between performance error with Shafer model (PE-Shafer) and total body weight (TBW). For any given body weight, this factor may be multiplied by the plasma concentration of fentanyl that is displayed by STANPUMP to more closely approximate actual plasma concentration. (*B*) 1/Correction factor *versus* TBW (from PE-Shafer data). This nomogram can be used to correct the desired target plasma concentration of fentanyl to be entered in STANPUMP during target-controlled infusion. For example, to achieve a target concentration of 1 ng/ml in a patient weighing 160 kg, 2.0 ng/ml would be entered as a target concentration. (*C*) *Solid line* = pharmacokinetic mass derived from the nonlinear regression analysis of PE-Shafer *versus* TBW. *Pharmacokinetic mass* = 52/Correction factor. This nomogram provides suggested dosing weights to be used to correct patient TBW to a more appropriate pharmacokinetic mass. *Dashed line* = pharmacokinetic mass derived from the nonlinear regression analysis of performance error with Scott model (PE-Scott) *versus* TBW.

Comparisons of predictive accuracy within and between Groups L and O are shown in table 4. In Group L, median PE and median APE of CP-Shafer were −19% and 23%, respectively. Although median PE of the Shafer program was negative, 64% of the Cp-Shafer values were within ±30% error. Median PE and median APE of Cp-Scott were 11% and 22%, respectively. The Scott and Stanski parameters underpredicted plasma concentrations in lean patients. The difference between the mean values for PE-Shafer and PE-Scott, −17% and 15%, respectively, was statistically significant. The accuracy of the corrected programs using regression analysis (Cp-Shafer-reg and Cp-Scott-reg) was superior to that of the original Shafer and Scott and Stanski programs, respectively.

In Group O, median PE and median APE of Cp-Shafer were −45% and 45%, respectively. Ninety-nine percent of PE-Shafer values were negative, and only 24% of Cp-Shafer values were within ±30% error. PE values of the original Shafer model in Group O were significantly more negative as compared with those in Group L and the mean value of APE was significantly larger than that in Group L. The median PE and median APE of Cp-Scott were −25% and 31%, respectively. The mean values of PE and APE for CP-Scott in obese patients were statistically different from the corresponding values for Cp-Shafer. Correction of the original predictions using the formula obtained from regression analysis (Cp-Shafer-reg and Cp-Scott-reg) improved both the bias and precision of prediction compared with those of the original models in all but one comparison; there was no difference between mean APE for Cp-Scott and Cp-Scott-reg (table 4).

The application of nonlinear regression analysis for prediction and correction of PE for fentanyl dosing was evaluated by creating a random division of the entire patient population into a "training" group and a "testing" group. PE-Shafer bias values for mean PE and median PE for the original data in the training group were −27.25% and −29.46%, respectively. A nonlinear regression equation for PE *versus* TBW was first determined using the training group data (fig. 4). That equation is as follows: PE-training (%) = $227.7 \times e^{-0.026\text{kg}} - 55.69$ (R squared = 0.662; $P < 0.001$).

This equation was then used to calculate corrected PE values for the data of the testing group as carried out for PE-Shafer and PE-Scott. The average bias values for mean PE and median PE for the testing group were −3.97% and −7.62%, respectively.

A comparison of clearance values between the lean and obese groups underscored the pharmacokinetic differences between the two groups (table 5). Average Cl (ml·kg^{-1}·min^{-1}) was 10.48 *versus* 8.76 for lean and obese patients, respectively, and average Cl (ml/min) was 718 and 986, respectively (lean *versus* obese). Both comparisons were statistically significant. The relationship between Cl (ml/min) and TBW (fig. 5A) showed a nonlinear profile similar to that of dosing weight (phar-

Table 4. Accuracy of the Shafer Model, Scott Model and Modified Programs for Predicting Plasma Fentanyl Concentrations in Lean and Obese Patients

	Group L (n = 277)				Group O (n = 188)			
	Cp-Shafer	Cp-Shafer-reg	Cp-Scott	Cp-Scott-reg	Cp-Shafer	Cp-Shafer-reg	Cp-Scott	Cp-Scott-reg
PE (%)								
Mean	−17*‡§	1	15*‖	−1	−45‡§	−3	−23‖	−3
Median	−19	−4	11	−3	−45	−7	−25	−9
SD	23	27	31	26	20	35	29	36
Within 30%	64	75	66	76	24	55	49	51
APE (%)								
Mean	24*‡	21	27†‖	21	45‡§	30	31	31
Median	23	18	22	18	45	28	31	29
SD	15	16	21	15	20	19	20	18

APE = absolute performance error; Cp-Scott, Cp-Shafer = predicted plasma fentanyl concentrations by the Shafer model and Scott and Stanski model, respectively; Cp-Scott-reg, Cp-Shafer-reg = modified predictions using correction factors derived from nonlinear regression; PE = performance error; Within 30% = percent of predictions within +/− 30% error.

Between-group comparisons: * $P < 0.001$ *versus* Group O; † $P < 0.02$ *versus* Group O. Within group comparisons: ‡ $P < 0.05$ *versus* Cp-Shafer-reg; § $P < 0.05$ *versus* Cp-Scott; ‖ $P < 0.05$ *versus* Cp-Scott-reg.

macokinetically equivalent mass) *versus* TBW (fig. 3C). Also, a strong linear relationship ($r = 0.793$, $P < 0.001$) was found between Cl (ml/min) *versus* pharmacokinetic mass (fig. 5B) with the intercept on the y axis approaching 0 Cl.

Statistically significant nonlinear relationships were found between PE-Shafer and BMI and between PE-Shafer and BSA. These results are presented in figure 6. A weak correlation ($r = -0.234$) was found between PE-Shafer and LBM, and essentially no correlation was found between PE-Shafer and ideal body weight ($r = 0.014$). No further analyses were included for these latter indices.

Discussion

The major objective of this study was an attempt to develop a continuous correction in the clinical doses required for fentanyl over the entire body weight range from normal to morbidly obese. The principal finding was that the non–weight-scaled pharmacokinetic models described by Shafer *et al.*[1] and Scott and Stanski[4] systematically overestimated fentanyl plasma concentrations as TBW increased. Highly significant negative correlations between PE-Shafer *versus* TBW and PE-Scott *versus* TBW (figs. 2A, 2B) and statistically significant differences for PE-Shafer, PE-Scott, APE-Shafer, and APE-Scott between Group L and Group O (table 4) support the above conclusion.

Slepchenko *et al.*[7] reported that a pharmacokinetic parameter set derived from a normal-weight population accurately predicted plasma sufentanil concentrations, on average, over a wide body weight range in morbidly obese patients (average BMI of 45.0; range, 35.0 to 52.6). They only examined obese patients. Although the average PE and APE values were favorable, they found a strong negative correlation between PE and BMI during sufentanil infusion over the entire weight range, indicat-

ing that increases of BMI contribute to an overestimation of the measured sufentanil concentration. From the linear regression equation that they reported for the relationship between median PE and BMI, a BMI of 35 was associated with a median PE of +18.4% and a BMI of 52.6 had a median PE of −23.8%. The total median PE spread over this range, therefore, was 42.2%. This is similar to the steep progression of increased negative PE values in our data over the same BMI range (fig. 6). Therefore, the study of Slepchenko *et al.* does not contradict the results of our study.

We have applied nonlinear regression analysis to model the relationship between PE and body weight for fentanyl over the body weight range encompassing normal weight adults and morbidly obese patients (figs. 2A
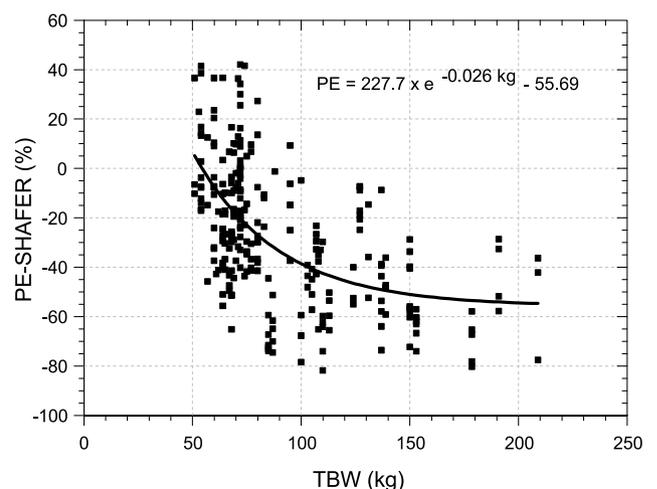

Fig. 4. Nonlinear regression analysis between performance error with Shafer model (PE-Shafer) and total body weight (TBW) for a random sample of approximately one half of the patients, termed the "training group." The equation for the relationship is: PE(%) = 227.7 × e$^{-0.026 \text{ kg}}$ − 55.69 (R squared = 0.662, $P < 0.001$). This equation was used to assess the improvement in the accuracy for prediction of plasma fentanyl concentrations in the remaining patients (the "testing group").

Table 5. Postoperative Clearance Data in Group L and Group O

	TBW (kg)	Sampling time median (min)	Clearance (ml/min)	Clearance (ml × kg^{-1} × min^{-1})	PK mass (kg)
Group L (n = 16)	68.5 (9.5)	1474	718 (163)†	10.48 (1.81)*	62.9 (6.8)
Group O (n = 10)	117.3 (33.4)	1461	986 (155)	8.76 (1.74)	87.9 (12.7)

Values are mean (SD) unless otherwise indicated.

PK mass = pharmacokinetic equivalent mass; Sampling time = time blood sampled for fentanyl concentration; TBW = total body weight.

* P = 0.025 vs Group O; † P < 0.001 vs Group O.

and 2B). From the relationships between both PE Shafer *versus* TBW and PE-Scott *versus* TBW, it can be interpreted that increases of TBW influence the pharmacokinetics of fentanyl in an exponential manner. The exponential equations for these relationships allow correction of Cp based on TBW. The corrected predicted values showed smaller biases (median PE) as compared with the original predictions of the Shafer and Scott and Stanski models and clinically acceptable accu-

racy (table 4). The nonlinear model also allowed for the development of nomograms that may have application in the clinical setting. Figure 3A presents the "correction factor" that may be applied to the displayed value for plasma concentration when the Shafer model is used to simulate plasma concentrations with STANPUMP. Figure 3B presents the factor that may be applied to the target concentration to correct for the effect of TBW in the situation where the Shafer model is being used for target-
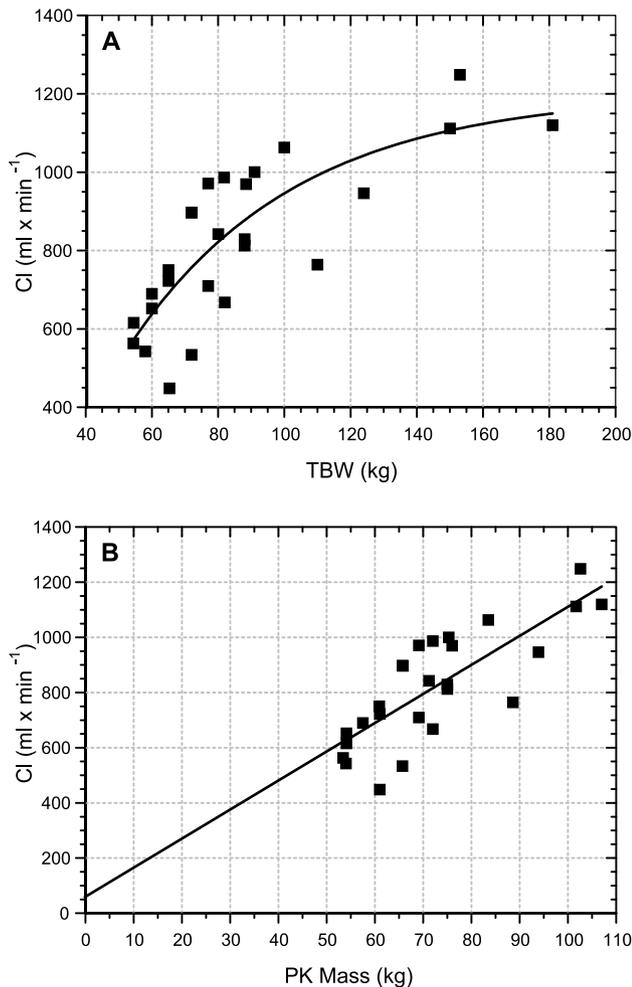

Fig. 5. (*A*) **Nonlinear relation between clearance (Cl) (ml/min) and total body weight (TBW). The equation for this relationship is as follows: Cl = −1851 × e** $^{−0.020\ kg}$ **+ 1201; r = 0.804; *P* < 0.001. (*B*) Linear relation between Cl (ml/min) and pharmacokinetic mass. The equation for this line is: Cl = 58.0 + 10.52 × kg; r = 0.793, *P* < 0.001. *PK mass* = pharmacokinetically equivalent mass.**
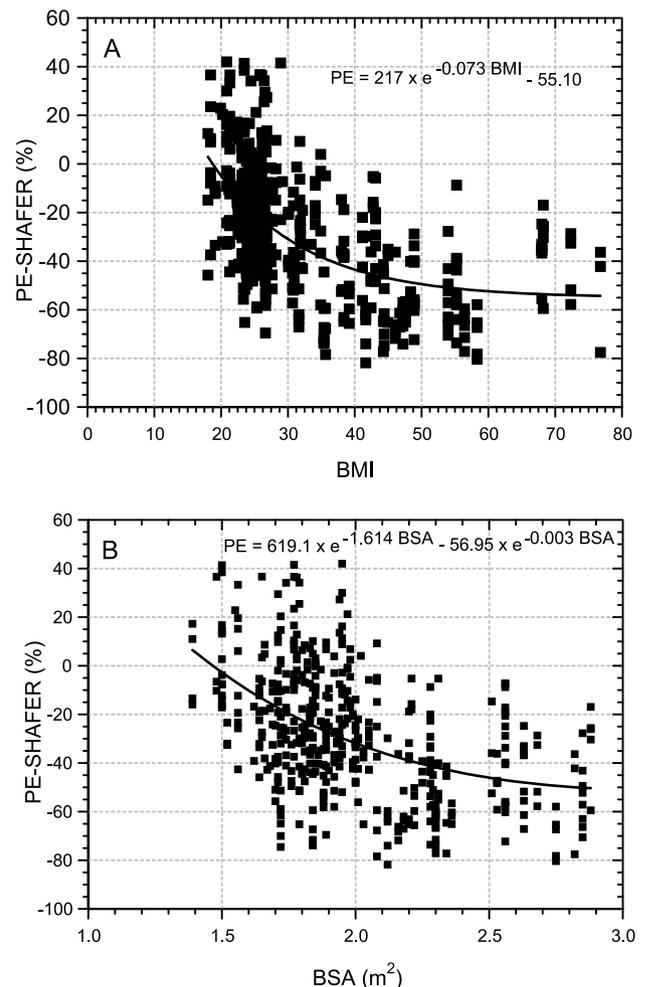
Fig. 6. (*A*) **Nonlinear regression analysis between performance error with Shafer model (PE-Shafer) and body mass index (BMI) (kg/m^2). This equation is: PE(%) = 216.7 × e** $^{−0.073\ BMI}$ **− 55.10; R squared = 0.697, *P* < 0.001. (*B*) Nonlinear regression analysis between PE-Shafer and body surface area (BSA). This equation is as follows: PE(%) = 619.1 × e** $^{−1.614\ BSA}$ **− 56.95 × e** $^{−0.003\ BSA}$**; R squared = 0.656, *P* < 0.001.**

Table 6. Correction factors and PK mass for Selected Total Body Weights

TBW (kg)	PE-Shafer-reg (%)	Correction Factor	1/Correction Factor	PK mass (kg)
52	0	1.00	1.00	52
70	−19	0.81	1.23	64
100	−37	0.63	1.59	83
120	−44	0.56	1.79	93
140	−48	0.52	1.92	100
160	−50	0.50	2.00	104
180	−51	0.49	2.04	106
200	−52	0.48	2.08	108

PE-Shafer-reg = performance error of the Shafer model obtained from regression analysis between performance errors and total body weights; PK mass = pharmacokinetic equivalent mass (i.e., suggested dosing weight for fentanyl) = 52/correction factor; = 52 × 1/correction factor; TBW = total body weight.

controlled infusion under an institutional approval. Figure 3C presents suggested dosing weights (termed "pharmacokinetic mass") to correct patient TBW for the apparent pharmacokinetically active equivalent when dosing is not being guided by computer software. The application of the nomograms to selected body weights is summarized in table 6.

Simply stated, pharmacokinetic mass quantifies the extent of departure from linearity that is observed for the relationship between appropriate dosing weight and actual body weight (TBW). This departure becomes substantial in the experience with morbidly obese patients. The nonlinear regression equation between PE-Shafer and TBW allowed for calculation of "correction factors" to translate the prediction of plasma concentration from non–weight-scaled pharmacokinetic models to actual body weight. These correction factors (fig. 3A) can be directly obtained by inspection of the trend line in the nonlinear regression plot in figure 2A. The factor in figure 3B for adjusting the target concentration in the non–weight-scaled model is the reciprocal of this correction factor. As we observed that there was no average bias in the prediction of plasma concentration at 52 kg TBW, we referenced all body weights to 52 kg, i.e., 52 kg/correction factor, to obtain a continuous series of pharmacokinetically equivalent body masses (pharmacokinetic mass) in relation to TBW (fig. 3C).

We have not placed equal emphasis on the results from the relationship between PE-Scott and TBW because the original data showed considerably greater variability than for PE-Shafer. The standard deviations for PE-Shafer and PE-Scott in lean patients were 23% and 31%, respectively, and 20% and 29%, respectively, in obese patients (table 4). However, when we used the correction factors from PE-Scott to calculate "pharmacokinetic mass-Scott," comparable to the Shafer-derived pharmacokinetic mass, the relationship to TBW was strikingly similar to the parameter derived from the Shafer data (fig. 3C). The only difference in the calculations was that the correction factors for PE-Scott were divided into 82 kg, which

is the approximate weight where there is no average prediction bias in PE-Scott data. The similarities in pharmacokinetic mass values derived from the rather widely different predictions of PE for the two pharmacokinetic data sets (figs. 2A and 2B and table 4) would appear to support the approach that we have taken to apply the nonlinear relationship between PE and TBW to derive correction factors that relate to the pharmacokinetically active mass.

To test the robustness of the nonlinear model, i.e., to evaluate the confidence with which it might be applied to patients outside our sample, we randomly divided the Shafer patient data into training and testing groups. The equation for the relationship between PE and TBW was similar to the result for the total population (fig. 4.). Application of the equation to correct PE in the testing group resulted in quite acceptable accuracy (−3.97% and −7.62% for mean and median PE, respectively).

In recent years, the number of morbidly obese patients undergoing surgery has increased in the United States. When most anesthesiologists are confronted with a patient weighing 200 kg, they must decide whether they should use a dose usually used in normal weight patients, use TBW as a dosing weight, or choose some dosing weight between normal weight and 200 kg. A dosing weight for fentanyl is usually chosen intuitively without any scientific guideline.[5] The suggested dosing weights (pharmacokinetic mass) derived from the current study could be useful for anesthesiologists who do not use computer software. The nomogram of dosing weights presented in figure 3C represents an exponential curve related to TBW. Suggested dosing weights may be read directly from this nomogram or interpolated from the data in table 6. Also, it can be noted that from 52 kg to approximately 100 kg (fig. 3C), pharmacokinetic mass increases almost linearly with a slope of approximately 0.65. Thus, for each increase of 10 kg TBW, 6.5 kg of dosing weight can be added to the reference body weight for dosing fentanyl. When TBW exceeds 140 kg, the pharmacokinetic mass curve flattens. For morbidly obese patients weighing 140 to 200 kg, dosing weights for fentanyl only range between 100 and 108 kg (table 6).

Many body mass covariates such as BMI and BSA increase with weight. Previously, we compared physiologic profiles between normal weight patients (mean 59 kg) and morbidly obese patients (mean 153 kg) during surgery (early and late stages) and postoperative stages (early and late stages) similar to the stages in the current study.[8] Cardiac output increased by 24 to 71% in morbidly obese patients as compared with lean patients, but when cardiac output and oxygen consumption were indexed to BSA, there were no statistical differences between the groups. Filling pressures of the right and left sides of the heart were increased in obese patients. Apparently, in obese patients, metabolic need during

anesthesia and at the resting state is adapted by increased cardiac output associated with increased filling pressure of the heart.

When we analyzed the associations between PE-Shafer and BMI and PE-Shafer and BSA, we found strong nonlinear relationships (R squared = 0.697 and 0.656, respectively) (fig. 6), similar to that for PE-Shafer *versus* TBW. It is possible to derive pharmacokinetic mass relationships to BMI and BSA that are similar to those for TBW; however, the pharmacokinetic "masses" in these cases would have the units of BMI and BSA, which would not be as easily transferred to dosing units as are kg units.

Cardiac output is an important parameter that affects the early pharmacokinetics of fentanyl distribution. Using the physiologic model for thiopental disposition, Wada *et al.*[9] observed that arterial concentrations of thiopental in the obese individual were 52% less over the first 5 min after a bolus and 73% less over 120 min. They attributed the differences to increased cardiac output and the capacity for thiopental uptake into fat. Bjorkman *et al.*[10] observed that larger cardiac output decreased arterial concentrations of fentanyl during the early phase after a bolus as compared with the model with normal cardiac output. When fentanyl is administered by continuous infusion, the influence of cardiac output may persist.[10] The late pharmacokinetics of fentanyl distribution are mainly affected by clearance. Henthorn *et al.*[11] observed that the sum of intercompartmental clearances for alfentanil pharmacokinetics were significantly correlated with the measured cardiac output. Obese patients have an increased proportion of body fat and increased muscle mass and body water.[6] These factors would increase the volume of distribution of lipophilic drugs such as fentanyl.[12,13] Schwartz *et al.*[13] reported that the total volume of distribution of sufentanil correlated linearly with the degree of obesity, expressed as percent ideal body weight. Although the pharmacokinetics of fentanyl have some important differences from those of sufentanil, alfentanil, or thiopental, as a lipophilic agent, fentanyl would be expected to share certain characteristics in regard to the influence of obesity.

LBM was reported to yield appropriate dosing weights for remifentanil administration even in cases of morbid obesity.[14] However, the formula used to calculate LBM appears to cause an artifact when the formula is applied to morbidly obese patients.[5] Therefore, there may be reservations in the use of LBM in obese patients. We found a weak correlation (r = 0.234) between PE-Shafer and LBM for fentanyl; however, the great differences between the pharmacokinetic characteristics of remifentanil and fentanyl do not permit a comparison between the studies.

In this study, we did not intend to derive a set of pharmacokinetic parameters for obese patients from our data. Sampling times were not optimized for pharmaco-

kinetic analysis but were dictated by the clinical need for blood gas analysis sampling. However, we observed that in patients who received prolonged postoperative infusions (usually for more than 20 h), predicted fentanyl concentrations did not change. This implied that a steady state had been reached. From relationships between measured fentanyl concentrations and the infusion rate of fentanyl at the time of sampling, we were able to calculate clearance from 16 patients in Group L and 10 patients in Group O (table 5 and figs. 5A and 5B). In these data, Cl (ml/min) increased in direct proportion to pharmacokinetic mass (fig. 5B) (r = 0.793, P < 0.001) but showed a nonlinear relationship to TBW (fig. 5A). Normalized clearance ($ml \cdot kg^{-1} \cdot min^{-1}$) also correlated with pharmacokinetic mass (r = −0.566, P < 0.003) (plot not shown). Of note in the data of table 5 was that the ratio of average Cl (ml/min) between Group L and Group O, 1.373 (986/718), was almost identical to the ratio for average pharmacokinetic mass between the groups, 1.398 (87.9 kg/62.9 kg), but was different from the ratio for average TBW, 1.712 (117.3 kg/68.5 kg). The clearance data imply that obesity influences the steady-state pharmacokinetics of fentanyl in an exponential manner and support the validity of pharmacokinetic mass for suggested dosing of fentanyl.

Although we did not directly evaluate the early pharmacokinetic characteristics of fentanyl from our data, PE-Shafer and PE-Scott were only moderately influenced by timing of sample during fentanyl infusion (table 3). The early PE values (Stage 1; <2 h) for both Shafer and Scott data were only different from the Stage 4 values (10–31 h). One explanation for the more negative PE values in the late postoperative period may be that the patients were wakeful and higher cardiac output may have contributed to decreased plasma concentrations of fentanyl. It should be noted that there were no differences in the ratios of the number of blood samples from lean and obese patients among the sampling periods; therefore, no bias would be expected in regard to observed differences in PE in the lean *versus* obese comparisons. The relative uniformity in PE over the entire sampling period suggests that the influence of obesity on early fentanyl pharmacokinetics might be largely similar to that at steady state. This is reasonable considering that clearance of the central compartment (total body clearance) would be expected to impact on all phases of dosing. Also, it may be noted that the average value for fentanyl Cl in our lean patients of 718 ml/min agrees well with values for the same measure in comparable weight patients, as follows: 620,[15] 772,[16] and 503 (Shafer) and 711 (Scott) from the STANPUMP program. However, it must still be considered a weakness in our study that we have not established the influence of obesity in the early minutes of fentanyl dosing, *i.e.*, in relation to anesthetic induction. Further study is necessary for this evaluation

but our findings may provide a starting point for that investigation.

In studies that examined the influence of age on fentanyl pharmacokinetics, Scott and Stanski[4] showed that the influence of advanced age on fentanyl pharmacokinetics is minor as compared to the influence of age on pharmacodynamics. The influence of sex on the pharmacokinetics of fentanyl was found to be insignificant.[10] It should be noted that our results and analyses might be influenced to some extent by the fact that our patients were undergoing major surgical procedures (table 2). Abdominal aortic cross clamping might have caused sequestration of fentanyl in the lower extremities. Also, blood loss may have affected cardiac output and distribution of fentanyl.

We measured plasma fentanyl concentrations during fentanyl infusion for surgery lasting 4 to 5 h and also during the postoperative period up to 31 h. Measured fentanyl concentrations were within a clinically acceptable range. Therefore, the results of the current study would be relevant for clinical anesthesiologists who use fentanyl in long-term cases.

In conclusion, both the Shafer model and Scott and Stanski model that use sets of pharmacokinetic parameters derived from normal-weight patients are not expected to predict plasma fentanyl concentrations for morbidly obese patients because morbid obesity is not represented in the pharmacokinetic data sets. We have observed that both models tend to overpredict measured plasma fentanyl concentrations as body weight increases from normal to morbid obesity. We used the nonlinear relationship between prediction error (from non–weight-scaled pharmacokinetic parameters) and body weight to identify correction factors that would cancel this error and could be translated to an appropriate pharmacokinetic body weight (pharmacokinetic mass) for dosing. The validity of pharmacokinetic mass was supported by the similarities in values derived from the rather widely different predictions of PE for the two pharmacokinetic data sets that were analyzed (PE-Shafer and PE-Scott). Finally, the strong linear correlation between total body clearance and pharmacokinetic mass over the entire body weight range contributes further confidence for the use of pharmacokinetic mass as a dosing approximation for fentanyl. It can be seen that fentanyl dose normalized to pharmacokinetic mass is more clinically useful than that based on TBW. Also, it might be expected that a nonlinear correction for body weight would be applicable for dosing certain other drugs in obese patients.

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