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Remifentanil Pharmacokinetics in Obese versus *Lean Patients*

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Background: **Remifentanil is a short-acting opioid whose pharmacokinetics have been characterized in detail. However, the impact of obesity on remifentanil pharmacokinetics has not been specifically examined. The goal of this study was to investigate the influence of body weight on remifentanil pharmacokinetics.**

Methods: **Twelve obese and 12 matched lean subjects undergoing elective surgery received a 1-min remifentanil infusion after induction of anesthesia. Arterial blood samples were collected for determination of remifentanil blood concentrations. Each subject's pharmacokinetic parameters were estimated by fitting a two-compartment model to the concentration *versus* time curves. Nonlinear mixed-effects population models examining the influence of lean body mass (LBM) and total body weight (TBW) were also constructed. Clinical simulations using the final population model were performed.**

Results: **The obese patient cohort reached substantially higher remifentanil concentrations. The individual pharmacokinetic parameters of a two-compartment model were not significantly different between the obese *versus* lean cohorts (unless normalized to TBW). The final population model scaled central clearance and the central and peripheral distribution volumes to LBM. The simulations illustrated that remifentanil pharmacokinetics are not grossly different in obese *versus* lean subjects and that TBW based dosing in obese patients can result in excessively high remifentanil concentrations.**

Conclusions: **The essential findings of the study are that remifentanil's pharmacokinetics are not appreciably different in obese *versus* lean subjects and that remifentanil pharmacokinetic parameters are therefore more closely related to LBM than to TBW. Clinically this means that remifentanil dosing regimens should be based on ideal body weight (or LBM) and not TBW. (Key words: Body weight; obesity; opioids; pharmacokinetics; remifentanil.)**

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REMIFENTANIL is a new fentanyl congener that has recently gained regulatory approval in the United States and elsewhere.[1] Because of its ester structure, remifentanil is susceptible to hydrolysis by blood and tissue esterases, resulting in rapid metabolism to essentially inactive products. Administered by continuous infusion, remifentanil's high clearance results in a rapid dissipation of opioid effect after an infusion is terminated.

Remifentanil's short-acting pharmacokinetic profile has been confirmed in several high resolution studies in elective surgical patients and in healthy volunteers.[2–5] Its context sensitive half-time (CST_{12}),[6,7] the time required for a 50% decrease in plasma or effect site concentration after termination of a continuous, steady state infusion, is approximately 4 min and is independent of infusion duration.

The effect of many patient demographic factors and comorbidities (*i.e.*, covariates) traditionally considered when formulating dosing schemes has also been examined for remifentanil. For example, remifentanil's pharmacokinetics are not appreciably altered by renal or hepatic insufficiency.[8,9] Similarly, gender does not impact remifentanil pharmacokinetics or pharmacodynamics.[10,11] With regard to age, like the other fentanyl congeners, remifentanil's central clearance and distribution

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volume are somewhat lower in the elderly population, whereas remifentanil potency increases with advancing age.[11]

Although total body weight (TBW) is a patient demographic factor on which dosing schemes for many drugs are based, its effect on remifentanil pharmacokinetics is not well known. In particular, the effect of obesity has not been investigated. The aim of this study was to investigate the effect of body weight on remifentanil pharmacokinetics using an open-label, single-dose, parallel group comparison study design in obese and lean patients undergoing elective surgery.

Materials and Methods

Recruitment, Instrumentation, and Safety Monitoring

After obtaining institutional approval and informed consent, 12 obese patients and 12 control patients matched for gender, height, age, race, and American Society of Anesthesiology (ASA) physical status classification were enrolled. All enrollees were scheduled for elective, non-cardiac, non-intracranial surgery with general anesthesia.

Only English-speaking men and women aged 18–60 yr who were ASA physical status I–III were eligible for enrollment. Obese patients were at least 80% more than their ideal weight based on criteria described by Abernethy and Greenblatt.[12] Matched control patients were within 20% of their ideal weight and were within ±5 yr (age) and ±10 cm (height) of their obese cohorts.

Potential subjects were excluded if they had a history of alcohol abuse or illegal drug use, a habit of tobacco use of more than 20 cigarettes per day, a history of hypersensitivity to opioids, or a record of significant psychiatric illness. Patients with renal or hepatic disease were also excluded, as were patients whose concurrent medications included drugs that are known to interact significantly with opioids. Patients who had had an anesthetic within 4 weeks of surgery were also not allowed to enroll.

To confirm eligibility, each subject underwent a detailed interview and a screening physical examination. Potential subjects whose airway anatomy on physical examination suggested the possibility of difficult direct laryngoscopy were not enrolled.[13] Subjects underwent a battery of laboratory tests to exclude significant illness, including serum chemistries, liver and renal function tests, a complete blood count, and urinalysis. All subjects had an electrocardiogram before enrollment, and all female patients received a urine pregnancy test to rule out pregnancy.

Before inducing anesthesia, patients received up to 3 mg of midazolam intravenously as a premedication. After attachment of the ASA-recommended safety monitors and adequate preoxygenation, anesthesia was induced with 3–7 mg/kg of intravenous sodium thiopental, and tracheal intubation was facilitated with intravenous vecuronium, 0.075–0.1 mg/kg. After induction of anesthesia and intubation of the trachea, anesthesia was continued with 66% nitrous oxide in oxygen and 0.4–2% isoflurane as needed.

After the anesthetic was underway an additional intravenous catheter for the administration of remifentanil was inserted into an upper extremity vein, and a radial artery catheter was placed for the collection of blood samples. Before remifentanil administration each patient received 0.2 mg of glycopyrrolate intravenously to prevent opioid-induced bradycardia.

Approximately 10–15 min after induction of anesthesia, each patient received 7.5–10 μg/kg of remifentanil intravenously over 1 min (note that 10 μg/kg is a very large dose of remifentanil that was intended to make remifentanil measurable in blood for an extended period; such a large dose should not be used clinically). Remifentanil was administered as a constant rate infusion by a laboratory syringe pump (Harvard Apparatus XG2000, South Natick, MA).

After termination of the remifentanil infusion, anesthesia was maintained with isoflurane, fentanyl, and vecuronium. The details of adverse events associated with remifentanil administration were recorded as they occurred.

Blood Sample Processing and Concentration Assay

Arterial blood samples of 3 ml were obtained at preset intervals with the most rapid sampling immediately after termination of the infusion. Samples were collected at the end of the infusion (*i.e.*, 1 min) and at 2, 3, 4, 5, 6, 7, 8, 10, 12, 15, 20, 25, 30, 40, 60, 90, 120, 180, 240, 300, and 360 min after starting the infusion. A maximum of 23 blood samples were drawn.

Because of remifentanil's metabolic pathway, special processing was necessary to prevent continued metabolism of remifentanil after sample collection. The details of our sample-processing technique have been described previously.[4]

Remifentanil blood concentrations were measured by a high-resolution, gas chromatographic, mass spectrom-

etry assay with a quantitation limit of 0.1 ng/ml and an interassay coefficient of variation of less than 15% for concentrations more than 0.1 ng/ml. Tetradeuterated remifentanil was included in the collection tubes as an internal standard to correct for variations in recovery among samples.[14]

Pharmacokinetic Analysis

The raw concentration *versus* time data were analyzed using several techniques. First, each individual patient's pharmacokinetic parameters were estimated. These individual parameter estimates were then plotted against several indices of body habitus (*i.e.*, patient covariates) to identify relationships that might be used to improve the final population model. A mixed-effects population approach based on the NONMEM** software was then used to build the final population model incorporating patient covariates. Finally, computer simulations including the context sensitive half-time were completed to bring clinical meaning to the mathematically based pharmacokinetic analysis. Because it had been previously demonstrated for the remifentanil dose range used in this study, linear pharmacokinetics were assumed for the purposes of this analysis.[2,4]

Individual Compartmental Analysis

Using the "two-stage" approach implemented on NONMEM, both two and three compartment mamillary models were fit to the raw concentration *versus* time data to estimate each volunteer's pharmacokinetic parameters. These biexponential and triexponential disposition equations were parameterized in terms of clearances and apparent distribution volumes. Initial parameter estimates were obtained from our previous work.[5] Because the magnitude of the errors between the measured concentrations (C_m) and the concentrations predicted (C_p) by the model were presumed to be proportional to the predicted concentration, a proportional ($^1/_{C_p^2}$) variance model was used for each fit.

After obtaining estimates for the individual volumes and clearances from nonlinear fitting, the alternative compartmental model parameters (*e.g.*, micro and macro rate constants) for each person were calculated using standard equations.[15] The population parameters from this two-stage approach for the obese and the lean groups were calculated by averaging the values obtained from the individual fits. This method is called the two-stage approach because the analysis proceeds in two stages. Pharmacokinetic parameters are first estimated for each volunteer by nonlinear regression, and these individual estimates are subsequently averaged to obtain the mean population estimates.[16]

The raw and TBW normalized parameters from the obese and lean groups were contrasted graphically and tested for significant differences using a nonparametric, two-tailed Student's t test assuming unequal variance (*e.g.*, Mann-Whitney rank sums test). Statistical significance was defined as a P value of less than 0.05.

Exploration of Parameter–Covariate Relationships

The individual pharmacokinetic parameter estimates from the two- stage analysis were regressed independently on each covariate as advocated by Maitre *et al.*[17] Total body weight (TBW) and lean body mass (LBM) were the covariates examined. LBM was calculated as advocated by Morgan and Bray.[18] These linear regressions were completed through the origin and also with an intercept term. The goal of this step was to identify relationships that might eventually be included in the final NONMEM population model. This step was also intended to help characterize the shape of these relationships between model parameters and the covariates.

Nonlinear Mixed Effects Model Analysis

In contrast to the two-stage approach, wherein the population pharmacokinetic model is obtained by averaging the parameters estimated from individuals, NONMEM simultaneously analyzes an entire population's data and provides estimates of typical values for the parameters along with an estimate of the parameter's interindividual variability within the population studied.

Interindividual error on each parameter was modeled using a log-normal error model:

$$\Theta_{individual} = \Theta_{typical} e^{\eta individual}$$

where $\Theta_{individual}$ is the true value in the individual, $\Theta_{typical}$ is the population mean estimate, and $\eta_{individual}$ is a random variable whose distribution is estimated by NONMEM with a mean of zero and a variance of ω^2. The estimates of ω obtained with NONMEM are similar to the coefficient of variation (CV) often used in standard descriptive statistics. Residual intraindividual error was modeled assuming a constant coefficient of variation.

Two- and three-compartment mamillary models without covariates were fit to the remifentanil concentration

** Beal SL, Sheiner LB: NONMEM User's Guide. San Francisco, University of California, San Francisco, 1979.

versus time data with NONMEM using the "first order conditional estimation" method and the "η-ϵ interaction" option. Model parameterization and initial parameter estimates were identical to those used with the two-stage approach.

Model Expansion with Covariate Effects

After obtaining the best NONMEM model without covariates, the influence of TBW and LBM on the model were then examined. Guided by the initial regression analysis exploring the relationship between model parameters and patient covariates, the final model was built using a stepwise approach in which individual covariate effects on each model parameter were incorporated into the model, and the resulting expanded model was examined for significant improvement. A -2 times the log likelihood (-2 LL) change of at least 4 was viewed as sufficient justification to include an additional parameter in the model (in the form of a covariate or a covariate plus a constant that represented the addition of two model parameters). Thirty-two different models were tested. The various models were tested forward (starting with no covariates) and backward (starting with all covariates) to confirm that the observed improvement was not a result of covariate correlation.

The performance of the various population models constructed by NONMEM was assessed in terms of the ability to predict the measured blood concentrations. This was quantitatively accomplished by computing the weighted residuals (WRs). A WR is the difference between a C_m and the C_p in terms of C_p. Thus, WR can be defined as:

$$WR = \frac{C_m - C_p}{C_p}$$

Using this definition, the WRs for all the NONMEM population models tested were computed at every measured data point.

Making use of the WR calculations, the overall inaccuracy of the model was determined by computing the median absolute weighted residual (MDAWR), defined as:

$$MDAWR = \text{median } |WR_1|, |WR_2|, \ldots, |WR_n|$$

where n is the total number of samples in the study population. Using this formula the MDAWRs for the population models constructed by NONMEM were computed for each model tested. The median weighted residual (MDWR), a measure of model bias, was also computed for each model. The performance of the models was also visually assessed by plotting the C_m/C_p *versus* time and examining the plots for accuracy and bias.

Computer Simulations

Computer simulations using the final pharmacokinetic model from NONMEM were performed to illustrate the clinical implications of the NONMEM analysis when applied to obese and lean patients. The first simulation predicts the time necessary to achieve a 50% and 80% decrease in plasma concentration after termination of a variable length infusion targeted to a constant drug concentration. These simulations, referred to as the context sensitive half-time (50% decrement time) and the 80% decrement time,[6,7,19] are based on Euler's solution to the two-compartment model with a step size of 1 s. The simulations were performed for a lean woman (125 pounds or $\approx$57 kg) and an obese woman (350 pounds or $\approx$159 kg) of the same height (5 feet, 5 inches) to contrast the pharmacokinetic implications of body habitus in widely different size patients.

The second simulation predicts the effect site concentrations that result from a typical remifentanil dosing regimen (1 μg/kg bolus injection followed by an infusion of 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 15 min and 0.25 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for an additional 105 min), contrasting the levels obtained in obese and lean women (as described previously) when dosage is formulated based on TBW or LBM using the final NONMEM model. The k_{e0} (rate constant characterizing the equilibration between the plasma and the effect site concentrations) used for these simulations was obtained from our previous work.[5] The simulated anesthetic is a "balanced" anesthetic in which the remifentanil dosing scheme is targeted to achieve levels that would be appropriate for remifentanil when used in combination with nitrous oxide, inhaled anesthetic vapor, or propofol.

Results

Recruitment, Instrumentation, and Safety Monitoring

Twenty-four of 25 patients enrolled completed the study. One patient who consented to enroll as an obese subject did not receive remifentanil because he presented an unanticipated difficult laryngoscopy after induction of anesthesia. This subject was awakened shortly after the induction of anesthesia and received a spinal anesthetic. Table 1 summarizes the

Table 1. Patient Demographic Features

Patient Number	Dose (μg)	TBW (kg)	LBM (kg)	Height (cm)	Gender	Age (yr)	ASA
Obese group							
1	1,236	124	54	170	F	32	2
2	840	84	48	157	F	36	2
3	968	97	45	154	F	36	2
5	900	118	55	170	F	49	2
6	1,020	136	81	180	M	54	2
7	780	105	56	170	F	33	1
8	800	107	58	173	F	36	3
9	720	95	54	168	F	30	2
12	920	123	54	170	F	29	2
14	900	120	77	178	M	32	1
16	1,050	140	84	183	M	44	2
17	820	110	75	178	M	47	1
Average	913	113	62	171		38	2
SD	141	17	14	9		8	1
Lean group							
4	450	61	46	168	F	32	2
10	450	60	46	173	F	45	1
11	460	60	40	150	F	36	1
13	470	63	46	165	F	35	1
15	600	82	66	183	M	33	2
18	630	78	64	185	M	44	2
19	550	70	59	180	M	53	2
20	415	55	42	163	F	36	2
21	340	49	38	159	F	34	2
22	550	77	61	173	M	43	2
23	425	57	43	165	F	30	2
24	435	57	45	173	F	38	2
Average	481	64	50	170		38	2
SD	84	10	10	10		7	0

TBW = total body weight; LBM = lean body mass.

demographic characteristics and ASA physical status classification of the patients. It is important to note that the two groups were grossly different in terms of TBW.

Initially subjects received 10 μg/kg of remifentanil. Because two obese subjects experienced pronounced bradycardia at that dosage, the protocol was modified so that the remifentanil dose was calculated at 7.5 μg/kg for the balance of subjects. The bradycardia (heart rate of approximately 35 beats/min) experienced by these two patients was accompanied by moderate hypotension and responded rapidly to atropine administration.

With the exception of nausea, vomiting, and mild hypotension, complications that were anticipated as part of this protocol, there were no other adverse events associated with remifentanil administration. No remifentanil infusion was terminated early because of an adverse event.

Pharmacokinetic Analysis

The infusion scheme applied in this protocol resulted in concentration *versus* time curves characteristic of brief infusions. The raw pharmacokinetic data are shown in figure 1. The obese patient cohort reached substantially higher peak concentrations and exhibited higher levels throughout much of the experiment.

Individual Compartmental Analysis

The raw concentration *versus* time data were adequately described by a two-compartment model. Remifentanil's clearance, approximately 3 l/min (a mean of 3.1 l/min in the obese group and 2.7 l/min in the lean group), is substantially greater than hepatic blood flow; this estimate of clearance is consistent with remifentanil's widespread extrahepatic metabolism. The estimates of remifentanil's distribution volumes (mean cen-

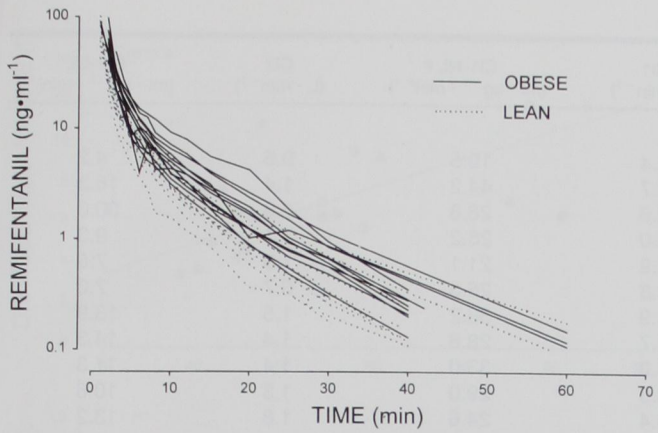

Fig. 1. The raw concentration *versus* time data. The obese subjects' data are plotted with a solid line; lean subjects are represented by the dashed line. Remifentanil concentration is shown on a log scale.

tral volume of 7.5 l and 6.8 l in the obese and lean groups, respectively, and mean peripheral compartment volume of 8.7 l and 7.6 l in the obese and lean groups, respectively) are somewhat less than expected for lipid-soluble molecules and revealed only modest distribution into body tissues. Table 2 displays the individual parameter estimates.

Comparison of the absolute volumes and clearances (*i.e.*, not weight normalized) from the obese and lean groups failed to reveal any statistically significant differences. However, when these parameters were normalized to TBW and compared, there were substantial differences between the lean and obese groups; these differences were all statistically significant as judged by the *t* test procedure as noted (table 2).

Exploration of Parameter–Covariate Relationships

Plots of the individual parameter estimates *versus* the covariates revealed that the parameters correlated better with LBM than TBW, although none of the relationships was particularly strong. Where a modest correlation was present, these relationships were best characterized by a straight line. Table 3 displays the results of these linear regressions, including the coefficients of determination (*i.e.*, r^2) and *P* values.

The most pronounced relationships, although modest, were between the volume of the central and peripheral compartments and LBM. Central clearance appeared to vary equally well with LBM and TBW, whereas the intercompartmental clearance did not correlate well with either covariate (*i.e.*, plots of the intercompartmental clearance *versus* LBM and TBW were complete "scattergrams"). The most demonstrable relationships are plotted (fig. 2).

Nonlinear Mixed Effects Model Analysis

The NONMEM population model parameter estimates are similar to the two-stage results. Table 4 displays the NONMEM parameters.

Model Expansion with Covariate Effects

The final (*i.e.*, best performing) NONMEM model included three covariate effects as suggested by the initial exploration of parameter *versus* covariate relationships. In the final model, central clearance, central distribution volume, and peripheral distribution volume were all scaled to LBM with an intercept term. Table 4 shows the typical parameter values for the expanded NONMEM model, including the covariate effects.

Addition of these covariate effects to the unscaled NONMEM model resulted in an improvement in the objective function from 320 to 275 but only slightly improved the MDAWR and the MDWR (a measure of bias). Table 5 shows these results, including the MDAWR 10th and 90th percentile values. Figure 3 shows the measured/predicted plots for the unscaled and expanded NONMEM population models.

Figure 3 calls attention to several important observations. First, the expanded NONMEM model results in only minimal improvement of the model performance compared to the unscaled model. Second, the models appear to be less accurate as time passes. And finally, the models appear to underpredict slightly the measured concentrations as evidenced by the slight trend toward a weighted residual that is positive overall. Thus, although the final model is statistically favored by NONMEM, for practical purposes it is not substantially better than the simple model (*i.e.*, no covariates model).

The results of several other covariate models that were tested deserve mention. Models that scaled all pharmacokinetic parameters to either LBM or TBW did not perform as well as the simple or "expanded" model in terms of MDAWR. Similarly, there was no significant improvement in the NONMEM objective function value for these models compared with the simple (no covariate) model. Tables 4 and 5 display the parameter values and goodness of fit measures for these somewhat more poorly performing models. Figure 4 displays the measured/predicted plots for these two models.

Table 2. Individual Parameter Estimates (Two-stage Approach)

Patient Number	V1 (L)	V1-NL (ml · kg^{-1})	V2 (L)	V2-NL (ml · kg^{-1})	Cl1 (L · min^{-1})	Cl1-NL (ml · kg^{-1} · min^{-1})	Cl2 (L · min^{-1})	Cl2-NL (ml · kg^{-1} · min^{-1})
Obese group								
1	2.5	20.3	4.3	34.9	2.4	19.5	0.5	4.2
2	10.8	128.7	9.3	110.5	3.7	44.2	1.4	16.3
3	6.5	67.3	10.3	106.7	2.6	26.8	2.9	30.0
5	4.0	33.9	6.3	53.3	3.0	25.2	1.1	9.3
6	6.4	47.2	7.2	52.6	2.9	21.1	1.0	7.6
7	6.4	61.3	6.5	62.6	2.8	26.3	0.7	7.0
8	9.6	89.5	10.7	100.2	3.9	36.2	1.5	13.9
9	6.3	66.2	8.2	86.7	2.7	28.6	1.4	14.3
12	7.0	56.8	8.1	65.8	4.0	33.0	1.4	11.3
14	11.9	99.3	12.3	102.4	3.5	29.0	1.3	10.6
16	11.9	85.2	14.6	104.5	3.4	24.6	1.8	13.2
17	7.1	64.5	6.7	61.1	2.2	20.5	0.8	7.2
Average	7.5	68.3*	8.7	78.4*	3.1	27.9*	1.3	12.1*
SD	3.0	29.3	2.9	26.2	0.6	7.1	0.6	6.7
Lean group								
4	4.9	81.3	5.2	85.4	2.3	38.7	0.8	12.7
10	6.2	104.0	5.9	99.1	2.8	46.5	1.1	17.9
11	3.6	60.4	9.1	151.9	2.1	35.8	2.1	35.0
13	4.6	73.7	5.0	79.9	2.1	33.2	0.9	14.0
15	13.9	170.0	16.2	198.4	3.6	43.9	2.3	28.7
18	12.9	165.9	14.2	182.4	4.2	54.0	2.1	27.2
19	5.7	81.1	8.1	115.1	1.9	27.3	0.8	11.6
20	5.0	91.0	7.3	132.1	2.7	48.3	1.2	21.5
21	3.4	68.6	4.9	99.8	2.3	47.4	0.6	12.2
22	9.2	120.3	8.5	110.4	3.6	46.6	1.4	17.8
23	7.5	132.0	3.2	56.0	2.4	43.0	0.5	9.4
24	4.3	74.8	4.1	72.7	2.4	42.6	0.8	13.6
Average	6.8	101.9*	7.6	115.3*	2.7	42.3*	1.2	18.5*
SD	3.5	37.3	4.0	43.7	0.7	7.4	0.6	8.0

V1 = central compartment volume of distribution; V2 = peripheral compartment volume of distribution; Cl1 = central compartment clearance; Cl2 = intercompartmental clearance; NL = normalized to total body weight.

* Significantly different parameters (obese *vs.* lean).

Computer Simulations

The context sensitive half-time simulations (50% decrement time) and the 80% decrement time simulations indicate that remifentanil's pharmacokinetics during infusion will be modestly influenced by the LBM mass of the patient. As displayed for the 50% and 80% decrement times (fig. 5), the values for obese patients (*i.e.*, patients with more *absolute* LBM) are somewhat lower, although not dramatically so, than those of lean patients. This implies that remifentanil may be slightly shorter-acting in the obese patient population when dosage is calculated based on LBM.

The simulation examining the concentration *versus* time profiles that result from TBW *versus* LBM dosing schemes suggest that dosage schemes based on TBW can

Table 3. Linear Regression Analysis of Total Body Weight (TBW) and Lean Body Mass (LBM) *versus* Individual Parameter Estimates

	Intercept	Slope	r^2	*P* Value
V1 *vs.* TBW	4.5	0.03	0.07	0.21
V1 *vs.* LBM	−0.9	0.14	0.35	0.03
V2 *vs.* TBW	4.7	0.04	0.11	0.12
V2 *vs.* LBM	0.1	0.15	0.31	0.02
Cl1 *vs.* TBW	2.1	0.01	0.16	0.05
Cl1 *vs.* LBM	1.8	0.02	0.16	0.02
Cl2 *vs.* TBW	1.0	0.00	0.02	0.57
Cl2 *vs.* LBM	0.9	0.01	0.02	0.56

V1 = central compartment volume of distribution; V2 = peripheral compartment volume of distribution; Cl1 = central compartment clearance; Cl2 = intercompartmental clearance; TBW = total body weight; LBM = lean body mass.

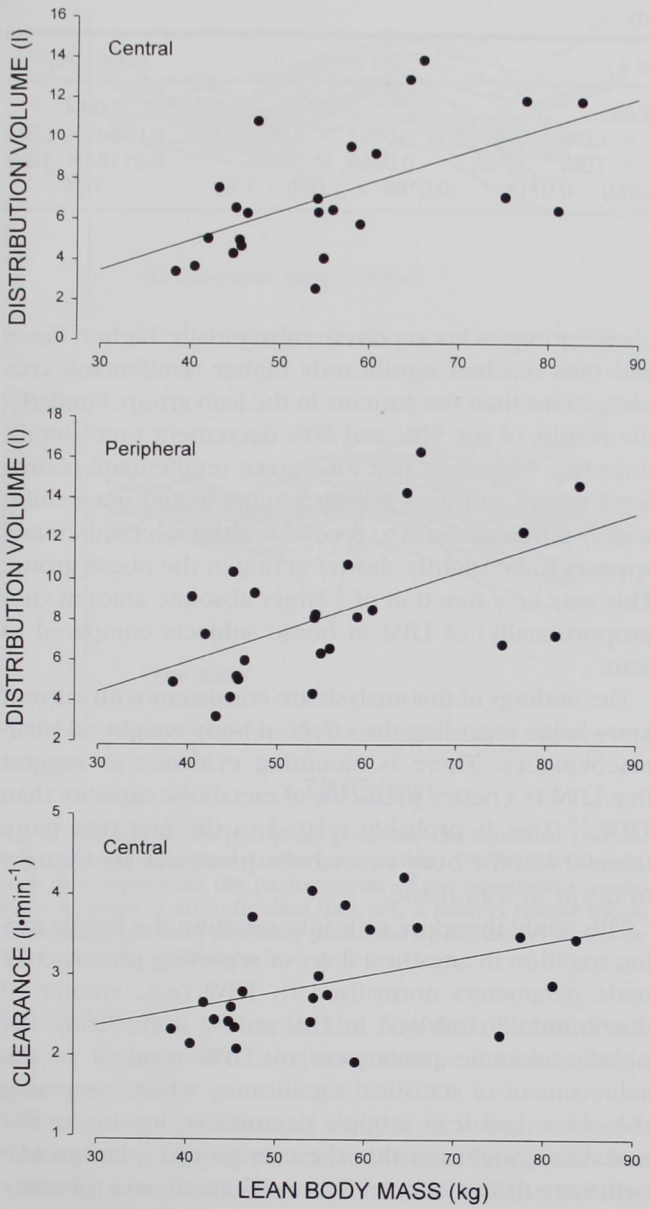

Fig. 2. Selected individual parameter estimates *versus* lean body mass (LBM). The top panel is a plot of the central volume of distribution *versus* LBM. The middle panel is a plot of the peripheral compartment volume of distribution *versus* LBM. The bottom panel is a plot of central clearance *versus* LBM. These relationships were incorporated into the final NONMEM population model.

result in a relative overdosage in obese patients. TBW-based dosing in an obese patient results in much higher effect site concentrations than does LBM dosing (fig. 6). In contrast, for lean patients, the concentrations that result from TBW-based dosing are not much greater than those based on LBM.

Discussion

Using an open-label, parallel group comparison design, this study has demonstrated that body weight is an important consideration in the formulation of remifentanil-dosing schemes. The essential finding of the study is that the absolute volumes and clearances (*i.e.*, parameters that are *not* reported per kilogram body weight) are similar in obese *versus* lean patients. A related finding is that simulated TBW-based dosing in obese patients results in excessively high remifentanil concentrations.

The clinical implications of this investigation are clear. Because remifentanil pharmacokinetic parameters appear to be more closely related to LBM than to TBW, remifentanil dosing should be based on LBM (or ideal body weight) rather than TBW. For practical purposes, because the estimation of LBM requires a somewhat cumbersome calculation that is not well suited to the clinical environment, ideal body weight (IBW), a parameter closely related to LBM and one that is perhaps more easily "guesstimated" by the clinician is probably an acceptable alternative.[18,20]

To the clinician in everyday practice, this simply means that all patients should be treated as though they are close to IBW when calculating remifentanil dosing schemes. Even substantially overweight and morbidly obese patients should receive remifentanil based on IBW. This translates into infusion rates of 0.2–1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and bolus doses of 0.25–1 μg/kg of IBW for most common "balanced anesthetic" applications. Detailed dosing recommendations for various clinical applications of remifentanil can be found elsewhere.[21,22] Incidentally, the bolus dose of 10 μg/kg used in this study was intentionally high to make remifentanil concentrations measurable for a long time; this dose should not be used clinically.

The raw data are perhaps the most straightforward evidence in support of these clinical recommendations. If TBW were an important marker of increased metabolic capacity or distribution, we would have expected the obese subjects to have achieved equal or somewhat lower concentrations compared with the lean group, assuming that TBW-based dosing represented "equipotent dosing." The obese group's concentrations were higher, and in some cases substantially higher, throughout most of the experiment (fig. 1).

The individual compartmental analysis provides the most compelling support of the conclusion that remifentanil dosing regimens should be based on LBM (or IBW). Unless the pharmacokinetic parameter values are nor-

Table 4. Selected NONMEM Population Models (Simple and Expanded)

	V1 (L)	V2 (L)	Cl1 (L · min^{-1})	Cl2 (L · min^{-1})
Simple model	5.97	8.85	2.86	0.94
All PRMS scaled to LBM	0.127 × LBM	0.175 × LBM	0.0551 × LBM	0.0184 × LBM
All PRMS scaled to TBW	0.0799 × TBW	0.110 × TBW	0.0356 × TBW	0.0118 × TBW
Final	(0.121 × LBM) − 0.0713	(0.165 × LBM) − 0.0713	(0.0185 × LBM) + 1.88	1.04

PRMS = parameters; LBM = lean body mass; TBW = total body weight.

malized to TBW, there is no statistically significant difference between the obese and lean groups for any parameter. Although there does appear to be a slightly greater variance among the obese group's parameter values, the overall mean values of the obese group are similar to those of the lean group.

Like the two-stage analysis, the NONMEM population approach is also supportive of LBM (or IBW) contingent dosing for remifentanil. As suggested by the plots of the individual parameter values *versus* the covariates (*i.e.*, LBM and TBW), scaling the parameters to TBW slightly worsened model performance, whereas scaling three of the four model parameters to LBM was statistically favored by NONMEM. It is important to note that the incorporation of covariates only minimally impacted the final model's performance. The inclusion of the additional parameters (*i.e.*, LBM plus a constant) was statistically justified in terms of the improvement of the NONMEM objective function value, but for practical purposes it did not greatly improve the model's usefulness.

The simulations also support the conclusion that remifentanil dosing ought to be based on LBM (or IBW) and not TBW. As illustrated in figure 6, calculating remifentanil dosage based on TBW in an obese patient results in concentrations that are grossly higher than those needed for clinical purposes.[23] This is in harmony with the observation that the only significant adverse hemodynamic events (*i.e.*, bradycardia with hypotension) of the study occurred in two patients from the obese group who received substantially higher doses and thus reached significantly higher remifentanil concentrations than the patients in the lean group. Similarly, the results of the 50% and 80% decrement time simulations (fig. 5) suggest that for a given remifentanil plasma level, obese and lean patient groups would not exhibit widely different times to recovery, although remifentanil appears to be slightly shorter acting in the obese group. This may be a function of a larger absolute amount (not proportionally) of LBM in obese subjects compared to lean.

The findings of this analysis are consistent with current knowledge regarding the effect of body weight on pharmacokinetics. There is mounting evidence to suggest that LBM is a better predictor of metabolic capacity than TBW.[18] This is probably related to the fact that more than 90% of the body's metabolic processes are thought to occur in lean tissue.[20]

This study therefore calls into question the long-standing tradition in anesthesiology of reporting pharmacokinetic parameters normalized to TBW (*e.g.*, volume of distribution in ml/kg). In this study, normalizing the pharmacokinetic parameters to TBW resulted in the achievement of statistical significance when comparing the obese and lean group's parameters, leading to the mistaken conclusion that the two groups' pharmacokinetics are truly different! For remifentanil, and for many other drugs used in anesthesia, normalizing pharmacokinetic parameters to TBW does not appear to be justi-

Table 5. The Median Absolute Weighted Residuals (MDAWR), the 10th and 90th MDAWR Percentiles, the Median Weighted Residual (MDWR), and the NONMEM Objective Function Values for Selected NONMEM Population Models

	Median (%)	10th Percentile (%)	90th Percentile (%)	MDWR (%)	Objective Function
Simple model	26.6	6.1	80.9	9.0	320
All PRMS scaled to LBM	29.9	4.7	89.5	5.8	317
All PRMS scaled to TBW	30.0	4.8	90.9	6.6	321
Final	23.1	4.2	69.8	3.1	275

PRMS = parameters; LBM = lean body mass; TBW = total body weight.

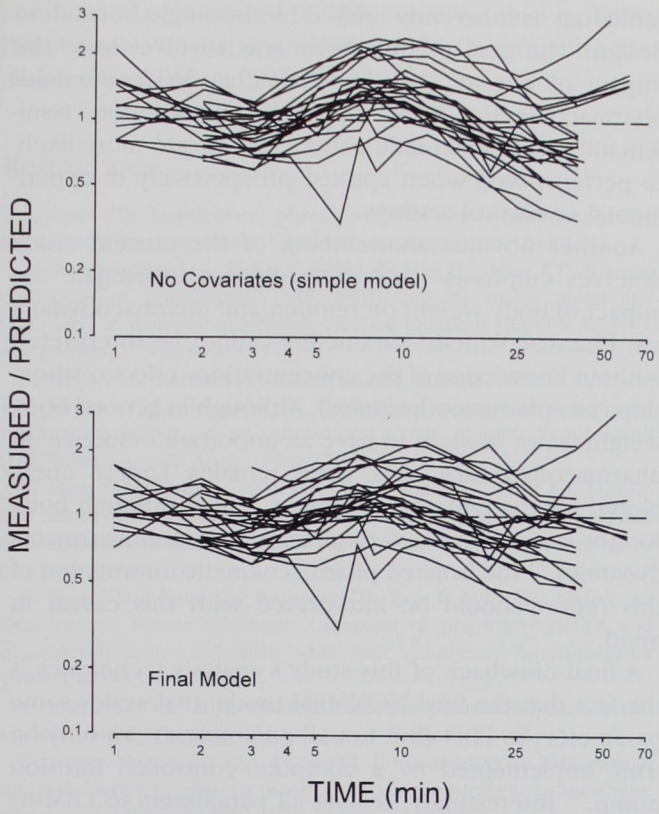

Fig. 3. The measured/predicted plots for the unscaled (no covariates) and the final (covariates added) NONMEM models. Each line represents the performance of the population model when applied to an individual data set. A subject whose blood concentrations were perfectly predicted by the model would be represented by a straight line at 1.

fied.[18,24-26] This is despite the fact that clinicians are much accustomed to calculating dosage for many drugs based on TBW.

Surprisingly, the effect of weight on the pharmacokinetics of the previously marketed fentanyl congeners has not been conclusively investigated. Much of the existing literature did not appear beyond abstract form. There are no formal manuscripts, for example, specifically designed to contrast the pharmacokinetics of fentanyl in obese *versus* lean subjects. With regard to sufentanil, a report by Schwartz *et al.* suggests that sufentanil exhibits more extensive distribution in obese patients, although this study reported TBW normalized parameters, and therefore the results must be interpreted with caution as demonstrated in the current study.[27] As for alfentanil, a sophisticated analysis by Maitre *et al.* of a large group of patients who received alfentanil suggests that the volume of the central compartment does correlate with TBW.[28] It is conceivable that the findings of the current study would not be fully applicable to the other fentanyl congeners because of remifentanil's unusual metabolic pathway.

The clinical relevance of this report is a function of the prevalence of obesity in western culture. Obesity is a common, major public health problem throughout the developed world. Since the early 1970s, the proportion of the American population that is overweight has steadily increased.[29] Among US adults aged 20–74 yr, approximately 25% are overweight with a slightly higher prevalence among women.[30] Almost 5% of US adults are morbidly obese, *i.e.*, they weigh twice their ideal weight. Anesthesiologists thus frequently encounter obese patients in everyday practice.

Despite the high prevalence of obesity and the fact that anesthesiologists formulate dosage regimens for many drugs based on TBW, studies on which anesthesiologists rely to guide dosing most often describe a drug's pharmacokinetics in healthy patients or volunteers who

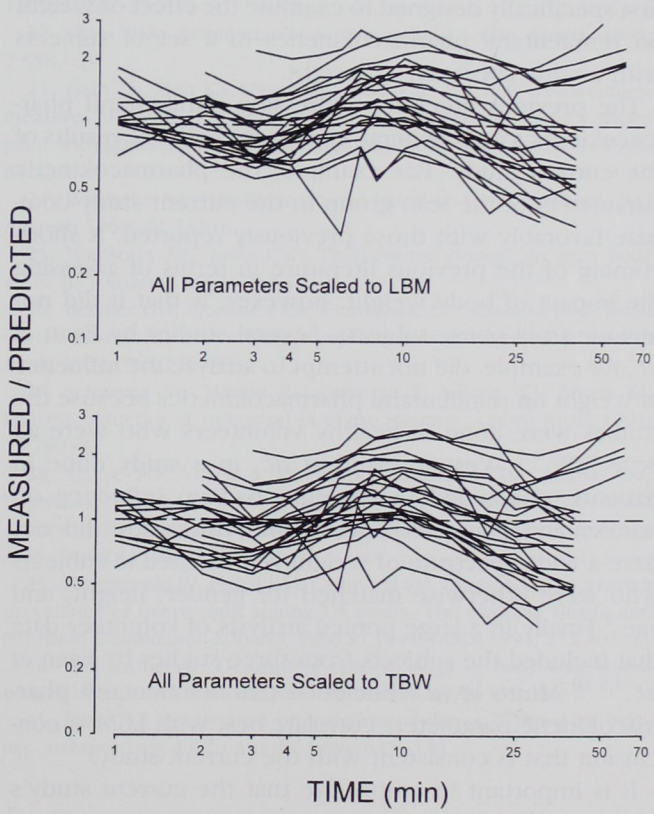

Fig. 4. The measured/predicted plots for the NONMEM models scaling all parameters to LBM and to TBW. Each line represents the performance of the population model when applied to an individual data set. A subject whose blood concentrations were perfectly predicted by the model would be represented by a straight line at 1.

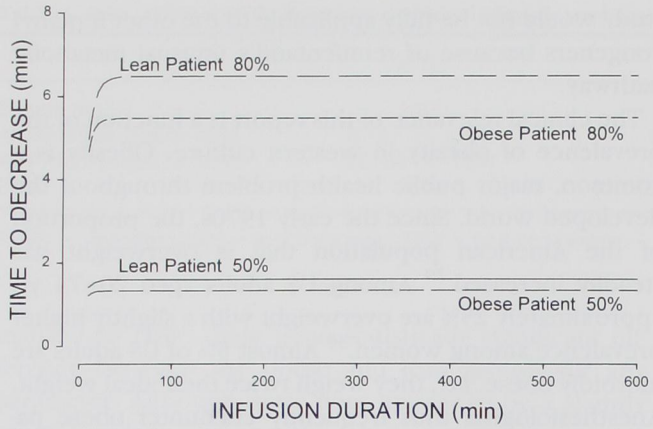

Fig. 5. A computer simulation of the context sensitive half-times (50% decrement times) and 80% decrement times of remifentanil in obese *versus* lean subjects. Note that in clinical terms the curves are not grossly different in obese *versus* lean subjects.

are close to IBW. This is certainly true of the previous remifentanil literature.[3,4,5,11] The current study is the first specifically designed to examine the effect of weight on remifentanil pharmacokinetics in a set of subjects with a wide spectrum of weight.

The previous literature addressing remifentanil pharmacokinetics is, in general, consistent with the results of the current study. For example, the pharmacokinetic parameters of the lean group in the current study compare favorably with those previously reported. A shortcoming of the previous literature in terms of assessing the impact of body weight, however, is that it did not include truly obese subjects. Several studies by Egan *et al.*, for example, did not attempt to analyze the influence of weight on remifentanil pharmacokinetics because the studies were done in healthy volunteers who were all near IBW.[4,5] Westmoreland *et al.*, in a study done in patients, concluded that weight had no influence on remifentanil pharmacokinetics, but this study did not have a wide spectrum of weight represented in subjects who were otherwise matched for gender, height, and age.[2] Finally in a large pooled analysis of volunteer data that included the subjects from three studies by Egan *et al.*,[4,5,10] Minto *et al.* concluded that remifentanil pharmacokinetic parameters correlate best with LBM, a conclusion that is consistent with the current study.[11]

It is important to emphasize that the current study's pharmacokinetic parameter set is not intended to compete with those from larger or more comprehensive studies (such as those found in Minto *et al.* and Egan *et al.*)[5,11] in which a diverse array of subjects received large doses of remifentanil for an extended period. The current study is inherently limited by the single bolus dose design. The goal of this study was to investigate the impact of obesity (*i.e.*, body weight) on remifentanil pharmacokinetics. Thus other "higher resolution" remifentanil pharmacokinetic parameter sets are more likely to perform well when applied prospectively in experimental or clinical settings.

Another obvious shortcoming of the current study deserves emphasis. This study did not investigate the impact of body weight on remifentanil pharmacodynamics. Pharmacokinetic parameters cannot be interpreted without knowledge of the concentration–effect relationship (*i.e.*, pharmacodynamics). Although in general body weight is not thought to have an important influence on pharmacodynamics, this issue remains largely unexplored for the fentanyl congeners. Thus, although body weight is not suspected to alter remifentanil pharmacodynamics,[11] the isolated pharmacokinetic information of this report should be interpreted with this caveat in mind.

A final drawback of this study's analysis techniques is the fact that the final NONMEM model that scales some parameters to LBM (but not all parameters) can only be truly implemented by a computer-controlled infusion pump.[31] Interestingly, scaling all parameters to LBM or TBW did not result in the best performing models.

In summary, this investigation has contrasted the pharmacokinetics of remifentanil in obese *versus* lean patients undergoing elective surgical procedures, demonstrating the remifentanil pharmacokinetic parameters

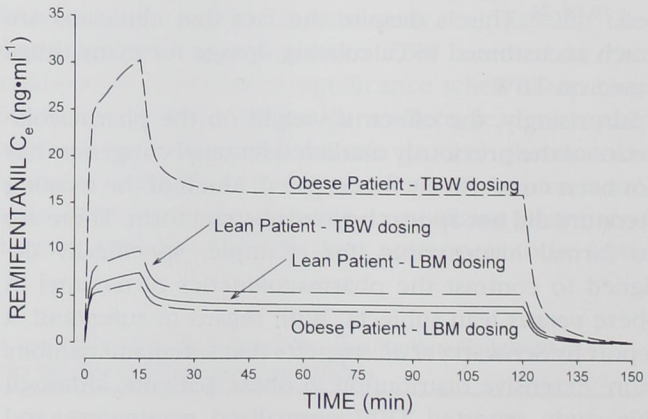

Fig. 6. A computer simulation of a typical remifentanil "balanced" anesthetic (*i.e.*, remifentanil in combination with nitrous oxide, inhaled vapor, or propofol) when the dosage regimen is calculated based on LBM or TBW for both obese and lean patients (1 μg/kg bolus injection followed by an infusion of 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 15 min and 0.25 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for an additional 105 min). Note that TBW-based dosing in an obese patient results in dramatically higher concentrations.

are more closely related to LBM (or IBW) than to TBW. Remifentanil dosing regimens should therefore be formulated on LBM or IBW, not TBW.

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