Performance of Target-controlled Sufentanil Infusion in Obese Patients

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Background: Because obesity might affect pharmacokinetic parameters, the authors evaluated the accuracy of target-controlled sufentanil infusion in morbidly obese patients using a pharmacokinetic model usually applied to a normal-weight population.

Methods: Target-controlled propofol and sufentanil coinfusions were administered to 11 morbidly obese patients (body mass index: $45.0 \pm 6.5 \text{ kg/m}^2$) undergoing laparoscopic gastroplasty. The target plasma propofol concentration was 3 μg/ml. The effect-site sufentanil target concentration was initially 0.4 ng/ml but was modified during surgery as a function of blood pressure and heart rate. Plasma sufentanil concentrations were measured from the onset of infusion until 24 h after its termination. The predicted sufentanil target concentrations were calculated by STANPUMP software. Intrasubject data analyzed included calculation of performance error, median performance error, median absolute performance error, divergence, and wobble. Pharmacokinetic analysis was performed using a nonlinear mixed effect model.

Results: Applied sufentanil target concentrations ranged from 0.3 to 0.65 ng/ml. The mean $\pm$ SD plasma sufentanil concentration measured during spontaneous ventilation was 0.13 ± 0.03 ng/ml. Median performance error (range) was -13% (-42 to 36%). Median absolute performance error was 26% (8–44%) during infusion and 17% (12–59%) for the 24 h after its completion. The pharmacokinetic sets used slightly overpredicted the concentrations, with a median divergence of -3.4% (-10.2 to 3.1%) during infusion. For body mass index greater than 40, the overestimation of plasma sufentanil concentrations was greater. A two-compartment model with proportional error for interindividual variability best fitted the data. The residual variability was modeled as an additive (0.016 ng/ml) or proportional error (23%). Clearance, central volume of distribution, intercompartmental clearance, and peripheral volume of distribution (coefficient of variation) were 1.27 l/min (23%), 37.1 l (20%), 0.87 l/min (44%), and 92.7 l (22%), respectively.

Conclusion: The pharmacokinetic parameter set derived from a normal-weight population accurately predicted plasma sufentanil concentrations in morbidly obese patients.

TARGET-CONTROLLED infusion (TCI) of anesthetic drugs has been investigated and successfully imple-

mented in clinical practice.[1] Averaged pharmacokinetic data sets derived from population samples of normal-weight patients are generally used. In obese patients, pathophysiological modifications are likely to affect drug tissue distribution and elimination.[2,3] So, doses for obese patients, calculated on pharmacokinetic data obtained from normal-weight individuals, might induce errors and overdoses.[4] Egan *et al.*[4] showed that administering an appropriate lean-person dose of remifentanil to obese patients induces deleterious side effects due to the excessively high plasma remifentanil concentration. Those authors concluded that, for opioids, lean body mass (LBM) should be a better predictor for calculating the drug dose needed. But LBM use has its limits since standard formulas or nomograms tend to overestimate LBM for obese patients. In addition, most of the published guidelines are based on total body weight.[5] Gepts *et al.*[6] found no relationships between sufentanil pharmacokinetic parameters and age, weight, or LBM and thus do not recommend adjusting its doses to weight or LBM. However, their conclusion might not be applicable to morbidly obese patients as none were included in the studied population. Thus, the aim of this study was to evaluate the accuracy of sufentanil TCI performance in obese patients undergoing laparoscopic gastroplasty and to determine the pharmacokinetic parameters for such a population.

Materials and Methods

This study was approved by the Nice University Ethics Committee (Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale, Nice, France). Written informed consent was obtained from 12 obese patients scheduled to undergo laparoscopic gastroplasty. Eight vertical-banded and four adjustable silicone gastric-banding gastroplasties were performed. Obese men and women aged 18–60 yr, with body mass index (BMI) greater than 35 kg/m^2 and American Society of Anesthesiologists physical status of I or II, were eligible for enrollment. BMI was defined as: body weight (kg)/height^2 (m). Exclusion criteria were as follows: a history of alcohol and illegal drug abuse, renal or hepatic disease or gastroesophageal reflux, concurrent medication with drugs known to interact with opioids or P-450 cytochrome. Subjects whose airway anatomy on physical examination suggested that direct laryngoscopy could be difficult were also excluded. Subjects underwent a battery of laboratory tests to exclude major illness or pregnancy,

including blood chemistries, liver and renal function tests, complete blood count, and urinalysis, as well as an electrocardiogram.

Anesthetic Procedure

One hour before surgery, patients received oral hydroxyzine (100 mg) as premedication. After local anesthesia (Emla® cream; Astra, Rueil-Malmaison, France) and noninvasive monitoring, the following blood vessels were cannulated: one forearm vein for administration of intravenous fluids, one forearm vein for administration of anesthetic drugs, and a radial artery for continuous monitoring of arterial blood pressure and for blood sampling. Saline solution was infused at a rate of 100 ml/h in addition to fluid replacement as indicated by the clinical context.

Diastolic, systolic, and mean (MAP) arterial pressures, heart rate (HR), and oxygen saturation measured by pulse oximetry (SpO_2) were recorded every 5 min from induction to extubation. MAP and HR baseline values were means of three rest values measured at 5-min intervals before induction.

After adequate preoxygenation, total intravenous anesthesia was induced and maintained with propofol and sufentanil using a TCI system. A bolus dose of atracurium (0.6 mg/kg) was given intravenously after onset of unconsciousness to facilitate tracheal intubation. During surgery, atracurium was continuously infused at a rate of $0.4 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$. Muscle relaxation was monitored with a train-of-four nerve stimulator. After intubation, the patient's lungs were ventilated with an air–oxygen mixture (50% oxygen), with maintenance of the end-expired carbon dioxide concentration at 4.5–5%. Warming blankets were used to maintain esophageal temperature at 35.5–36.5°C.

A TCI Diprifusor® (Zeneca, London, United Kingdom) was used for propofol infusion. For induction of anesthesia and intubation, the targeted plasma propofol concentration of 6 μg/ml was achieved within 2 min. During surgery, the target concentration was 3 μg/ml. Propofol TCI was discontinued at wound closure. The weight used to determine the propofol infusion rate was calculated using the following formula[7]: corrected weight = ideal body weight (IBW) + [0.4 × excess weight]. IBW was calculated with the formula of Lorentz: IBW = [height (cm) − 100 − (height − 150)]/4 for men and IBW = [height − 100 − (height − 150)]/2 for women; excess weight = measured weight − IBW.

Sufentanil TCI was administered with a BD Pilot Anesthesia® pump (Fresenius-Vial, Brezins, France) connected *via* a serial RS-232 interface to a personal computer running the STANPUMP software.# Unlike

propofol, no weight correction was made for sufentanil. The intercompartment transfer constants and the central compartment volume of distribution (Vc) were taken from the pharmacokinetic sets of Gepts *et al.*,[6] while the transfer constant k_{e0} between the central compartment and the effect site was from Scott *et al.*[8] The target effect-site sufentanil concentration for induction and maintenance of anesthesia was 0.4 ng/ml. We targeted the effect site for sufentanil to minimize the time to equilibrate the plasma concentration with the effect site; it took 6 min to obtain the targeted concentration. During surgery, the target concentration was adjusted to MAP and HR: Variation of both or either more than 15% above or below baseline values induced a 0.05-ng/ml increment of the target sufentanil concentration in the same direction. The predicted effect-site concentration had to reach the target before a new concentration change could be attempted. Sufentanil TCI was stopped at pneumoperitoneum exsufflation. Hypotension (MAP < 60% of baseline value) was treated with intravenous ephedrine. Atracurium was stopped 30 min before the end of surgery. Tracheal extubation was performed in the recovery room using the following criteria: spontaneous ventilation (rate > 10 breaths/min, SpO_2 > 98%, end-tidal pressure of carbon dioxide [P_{ETCO_2}] < 45 mmHg), opening eyes on verbal command and a train-of-four ratio greater than 0.8. Postoperative pain management included propacetamol (2 g, Prodafalgan®; UPSA, Rueil-Malmaison, France) administered 1 h before the end of surgery and, in the recovery room, incremental morphine doses as a function of pain assessed with a visual analog scale.

Blood Sample Processing and Sufentanil Assay

Arterial blood samples (4 ml) for measurement of plasma sufentanil concentrations were obtained immediately before the injection of sufentanil and 2, 5, 15, 30, 45, and 60 min after and then every 15 min until the end of the infusion. Additional samples were collected 5, 10, 20, 30, 45, 60, and 90 min and 2, 4, 8, 12, and 24 h after the end of the infusion. All blood samples were collected in heparinized tubes, and the plasma was separated (3,500 rpm for 10 min) and frozen (−75°C) until analysis. Plasma sufentanil concentrations were determined by radioimmunoassay, after extraction with solvent (n-heptane–isoamyl alcohol, 95/5 v/v).[9,10] The limit of quantification was 0.02 ng/ml. For a concentration range of 0.05–10 ng/ml, the interassay and intraassay coefficients of variation (CV) were less than 10% with 90% accuracy as assessed with quality-control samples prepared independently in blank human plasma and stored under the same conditions as patient samples.

Predictive Accuracy Analysis

The predicted target concentrations (effect site and plasma) and the corresponding sufentanil infusion rate were recorded every 10 s by the STANPUMP software.

The predicted concentrations were calculated by computing simulation 2 h after stopping the infusion. Data were analyzed using Excel 97 (Microsoft Corporation, Redmond, WA) and Statview 5.0 (SAS Institute Inc., Cary, NC). First, for each blood sample, the percent performance error (PE) of the predicted plasma sufentanil concentrations was calculated according to the formula: PE = (Cm − Cp)/Cp × 100, where Cm and Cp are, respectively, measured and predicted plasma sufentanil concentrations. PE gives an indication of the bias of the measured concentrations, and the absolute PE value is an estimation of the precision (inaccuracy). As recommended by Varvel *et al.*,[11] intrasubject data analysis consisted of an evaluation of four indicators of predictive performance for the n subjects (Appendix): (1) median PE (MDPE): the percent MDPE reflects the bias of TCI in the ith subject; (2) median absolute PE (MDAPE): the percent MDAPE indicates the inaccuracy of TCI in the ith subject; (3) divergence characterizes performance stability over time; and (4) wobble measures the intrasubject variability of PE. MDPE, MDAPE, and divergence were calculated for samples obtained during sufentanil infusion and the 24 h after its termination.

Population Pharmacokinetic Modeling

Concentration–time data were analyzed using a nonlinear mixed-effects model, as implemented in the program NONMEM.[12] Two- and three-compartment pharmacokinetic models with zero-order input and first-order elimination were tested to fit the data. The following models were used to describe the intersubject variability of the pharmacokinetic parameters: $P_j = P_{pop} (1 + \eta_{pj})$ proportional model; $P_j = P_{pop} + \eta_{pj}$ additive model; in which P_j is a kinetic parameter of the jth individual, P_{pop} is the population mean value of the parameter, and η_{pj} is the interindividual error, distributed normally with a mean of zero and variance equal to ω^2. Several error models (additive, proportional, or both) were applied to describe residual variability. A first analysis was performed to find the basic structural model that would best define the data. The model was selected on plots (measured *vs.* predicted concentration, weighted residuals *vs.* predicted concentration, weighted residuals *vs.* time), the value of the NONMEM objective function (goodness of fit), and the lowest estimate of the interindividual and residual variabilities. The basic model estimated the pharmacokinetic parameters without any covariates. Once it was established, the influence of each covariate (sex, age, height, body weight, and BMI) on the pharmacokinetic parameters was tested. The measured-*versus*-predicted concentration curve, the change of objective functions, and the change of parameter variability were recorded. A lower objective function value of at least 6.61 (chi-square distribution with one degree of freedom for $P < 0.01$) compared to the basic pharma-

cokinetic model was required for the inclusion of a single parameter in the model. Covariates that significantly reduced the objective function were then combined in a stepwise fashion until no further reduction of the objective function was obtained (full model). An intermediate multivariate model was then established including all significant covariates. Finally, to retain only the covariates with the best abilities to predict sufentanil concentration in a final model, an objective function change of at least 10.82 ($P < 0.001$) was required for a single parameter during backward stepwise multiple regression analysis.

Statistical Analysis

Descriptive statistics for predictive accuracy included means, SDs, 95% confidence intervals (CIs), medians, and the 10th and 90th percentiles. Indicators predictive of performance differ significantly from zero if their 95% CIs do not include zero. Least-squares linear regression was used to evaluate relationships among BMI, weight, age, and performance parameters and to evaluate the relationship between Cp and Cm. The Wilcoxon test was used for paired data. Inaccuracy, bias, and divergence were thus compared between the whole blood-sampling period, the infusion period, and the postinfusion period. Results are expressed as mean ± SD, as mean (range), or median (range). A P value less than 0.05 was considered significant.

Results

One patient was excluded because of a registration error of the doses administered by the STANPUMP software (disconnection between the computer and the

Table 1. Demographic Data

Variable	Mean ± SD (range)
Age (yr)	38.7 ± 11.1 (24–55)
Weight (kg)	125.4 ± 23.3 (82–155)
Body mass index (kg/m²)	45.0 ± 6.5 (35.0–52.6)
Duration of sufentanil infusion (min)	216 ± 104 (94–456)
Duration of propofol infusion (min)	253 ± 105 (125–486)
Total sufentanil dose (μg/kg)	1.2 ± 0.4 (0.7–2.1)
Total propofol dose (mg/kg)	18.5 ± 9.1 (8–38)

Table 2. Clinical Events during the Course of Anesthesia with Sufentanil

Clinical Event	Mean ± SD (min)
After starting sufentanil	
Loss of consciousness	2.6 ± 0.7
Tracheal intubation	6.3 ± 2.4
After stopping sufentanil	
Spontaneous ventilation	49.6 ± 17.5
Opening eyes	52.4 ± 18.9
Extubation	57.9 ± 19.3

Table 3. Accuracy of the Gepts Study and the Present Pharmacokinetic Models for Sufentanil Target-controlled Infusion into Obese Patients

Descriptive Statistic	Infusion	After Stopping the Infusion	Whole Period	
			Gepts Study	Present Study
Median	−6.8	−11.4	−12.8	8.4
Range	−43.6 to 28.2	−59.5 to 40.6	−42.0 to 35.6	−34.6 to 44.9
Mean	−5.1	−7.3	−6.6	8.8
% MDPE SD	23.2	27.8	24.0	25.5
95% CI (mean)	−20.3 to 10.1	−25.5 to 10.9	−22.3 to 9.1	−8.3 to 25.9
10th Percentile	−30.4	30.0	−33.8	31.5
90th Percentile	27.5	29.5	29.0	44.7
Median	26.3	16.9	19.8	30.8
Range	7.6 to 43.6	12.0 to 59.5	11.7 to 42.0	12.1 to 44.9
Mean	24.8	24.7	25.0	27.7
% MDAPE SD	11.8	14.5	10.5	11.7
95% CI (mean)	17.1 to 32.5	15.2 to 34.2	18.7 to 31.8	19.8 to 35.6
10th Percentile	13.8	15.0	14.5	12.7
90th Percentile	39.9	40.6	40.3	44.7

MDAPE = median absolute performance error; MDPE = median performance error.

electric pump). Demographic data are reported in table 1. The mean BMI of 11 patients was 45.0 ± 6.5 kg/m^2 (range, 35.0–52.6 kg/m^2). Clinical events occurring during anesthesia are summarized in table 2. Sufentanil concentrations were measured for a mean of 711 min (range, 240–1,440 min) during the postinfusion period. The range of the applied target sufentanil concentration was 0.3–0.65 ng/ml. The mean plasma sufentanil concentration measured between incision and wound closure was 0.39 ng/ml (range, 0.18–0.94). The mean $\pm$ SD sufentanil plasma concentration measured during spontaneous ventilation was 0.13 ± 0.03 ng/ml (range, 0.07–0.18 ng/ml). Target sufentanil concentrations were modified a mean four times (range, 2-10). Tables 3 and 4 show the results of the four calculated indicators (MDPE, MDAPE, divergence, and wobble) predictive of performance for the pharmacokinetic models during the whole study period, during and after sufentanil infusion. The median MDPE was negative, and the bias did not differ significantly from zero, as the 95% CI included zero. The MDAPE was 26.3% (range, 7.6–43.6%) during infusion and 16.9% (range, 12.0–59.5%) for the 24 h after the end of infusion. The pharmacokinetic sets used slightly overpredicted the concentrations, with a divergence negative value of −3.4% (95% CI, −10.2 to 3.1%) during infusion.

Predicted sufentanil concentrations were significantly correlated with measured concentrations (fig. 1). Concentration-*versus*-time curves from the patients with the best, median, or worst performances of the sufentanil pharmacokinetic model are given in figure 2. As shown by the Cm/Cp-*versus*-time curves, sufentanil concentrations were not systematically overpredicted, especially during the first 240 min (fig. 3). Indeed, for some patients, the model underpredicted the measured sufentanil concentrations. There was a negative correlation between bias and BMI ($r^2 = 0.52$, $P < 0.05$), and sufentanil plasma concentrations being overestimated for BMI greater than 40 kg/m^2 (fig. 4). No relationship was found between BMI and inaccuracy, wobble, or divergence, or between each of the four indicators predictive of performance and weight.

A two-compartment model with drug-infusion input and first-order elimination best described the measured plasma sufentanil concentrations (fig. 5). With a three-compartment model, it was impossible to define all the interindividual variabilities, and the model appeared to be unstable. Thus, the two-compartment model was

Table 4. Divergence and Wobble of the Gepts Study and Present Pharmacokinetic Models for Sufentanil Target-controlled Infusion into Obese Patients

Descriptive Statistic	Infusion*	Divergence (%/h), After Stopping the Infusion	Whole period		Wobble (%)	
			Gepts Study	Present Study	Gepts Study	Present Study
Median	−3.4	1.9	2.6	0.2	15.1	19.8
Mean	−3.5	3.1	1.6	1.4	14.7	21.1
SD	10.2	4.9	4.1	2.7	5.3	5.2
95% CI (mean)	−10.2 to 3.1	−0.1 to 6.3	−1.0 to 4.3	−0.4 to 3.3	11.2 to 18.3	17.5 to 24.5
10th Percentile	−13.4	−1.7	−4.2	−0.1	9.7	14.1
90th Percentile	5.6	9.3	6.5	7.4	22.3	28.7

* $P < 0.05$ comparison between divergence during infusion and divergence for the whole period according to the Gepts model.
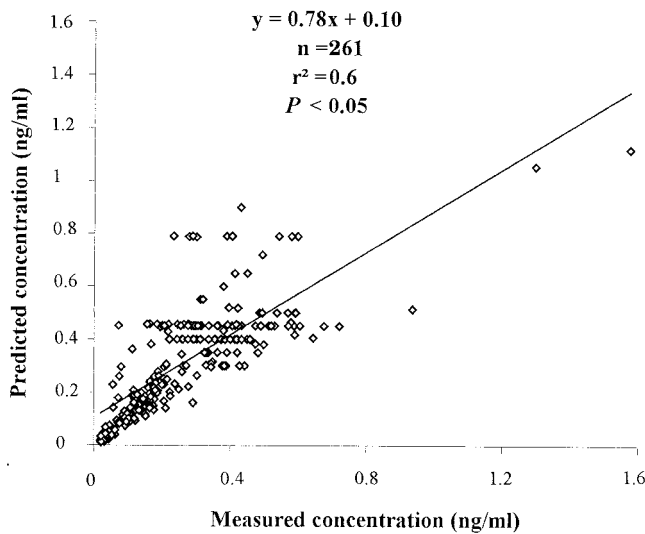
Fig. 1. Correlation between predicted and measured sufentanil concentrations using the Gepts model.

used to investigate whether the covariates could improve fit and decrease interindividual variability. The proportional error model was the most appropriate for intersubject variability, while the residual variability was modeled as an additive and a proportional error (table 5). The basic structural model was described with the following parameters: Cl, Vc, intercompartmental clearance (Q), and peripheral compartment distribution volume (Vp) (table 5). The terminal half-life ($t_{1/2\beta}$) based on microconstant pharmacokinetic parameters was approximately 2.23 h. None of the covariates tested (age, sex, height, body weight, BMI) significantly decreased the objective function or improved the predicted *versus* measured concentration, and thus none was retained in the final model. However, Cl tended to increase with BMI (fig. 6). The predictive accuracy analysis of our pharmacokinetic model is reported in tables 3 and 4.

Discussion

A mean 20–30% variation of measured concentrations above or below targeted anesthetic drug concentrations, with a maximum of 50–60%, can be considered clinically acceptable.[13] However, variability may result from a variety of different possible sources of variability in a TCI model. Particularly, patients receiving TCI do not necessarily belong to the same population as that to develop the original pharmacokinetic model. In moderately obese patients, pharmacokinetic differences have been reported for opioids, such as remifentanil[4] or sufentanil.[14] Consequently, applying a pharmacokinetic model derived from a population of normal-weight individuals could lead to errors in obese patients.[4] However, we found that a pharmacokinetic model–driven infusion device using the sufentanil pharmacokinetic parameters
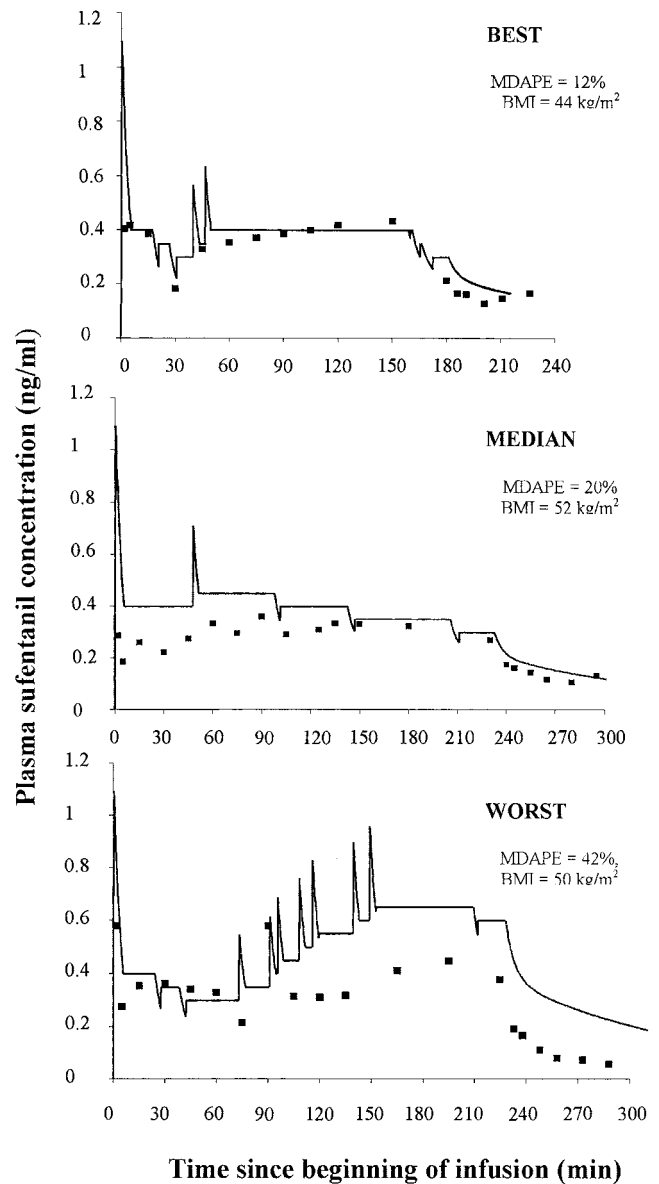

Time since beginning of infusion (min)

Fig. 2. Measured (squares) and predicted (lines) sufentanil concentrations in plasma over time from the patients presenting the best, the median, or the worst performance of the sufentanil pharmacokinetic model. BMI = body mass index; MDAPE = median absolute performance error.

described by Gepts *et al.*[6] performed well in morbidly obese patients and was adequate for sufentanil TCI.

Different standard definitions of overweight have been proposed.[15] Traditionally, obesity has been defined as body weight greater than 30% above IBW on standard height–weight tables. At present, it is usually defined in terms of BMI, with normal values of 23 kg/m² for men and 21 kg/m² for women. Our patients were morbidly obese (BMI > 35 kg/m²).[16]

The kinetics of plasma concentrations differ widely depending on whether the pump is targeting the effect site or the plasma. Because of the difficulty to rapidly change the drug effect while targeting the plasma, we
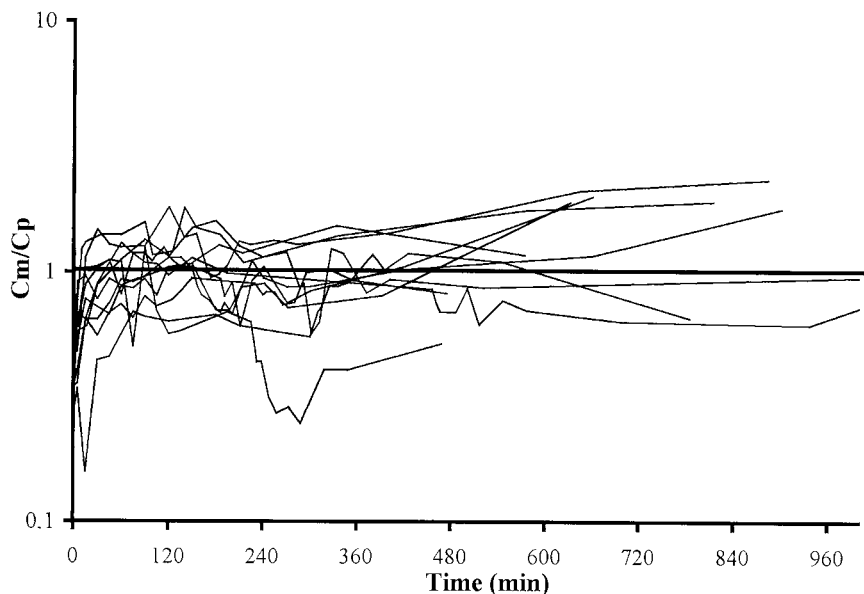
Fig. 3. Measured to predicted sufentanil concentration (Cm/Cp) ratios on a semi-logarithmic scale as a function of time. A Cm/Cp of 1 represents 100% accuracy.

targeted the sufentanil effect site. Propofol was chosen because of its good pharmacokinetic and pharmacodynamic properties for induction and maintenance of anesthesia in the obese.[7] Considering the moderately increased steady state plasma concentrations in obese patients during propofol infusion at constant rates (3, 6, and 9 $mg \cdot kg^{-1} \cdot h^{-1}$), some authors suggested that the combination of a fixed dose and a body weight–adapted dose would be preferable.[7,17] The target concentration and the corrected weight we used provided adequate anesthetic levels without marked hemodynamic effects.[7,17]

Recovery of consciousness is governed not only by the decrease of the propofol effect-site concentration relative to the opioid effect-site concentration, but also by the pharmacodynamic interaction between these agents.[18] In combination with propofol (3 μg/ml), a

sufentanil effect-site concentration of 0.4 ng/ml achieved "deep" anesthesia with more rapid recovery of consciousness than with alfentanil or fentanyl.[18] During surgery, the sufentanil concentrations we measured were similar to those necessary to reduce the isoflurane
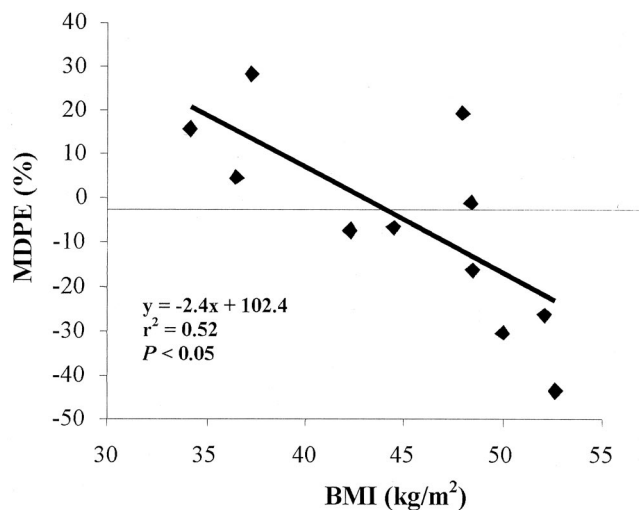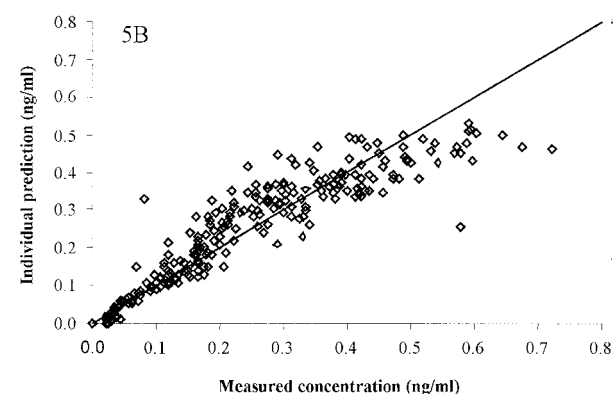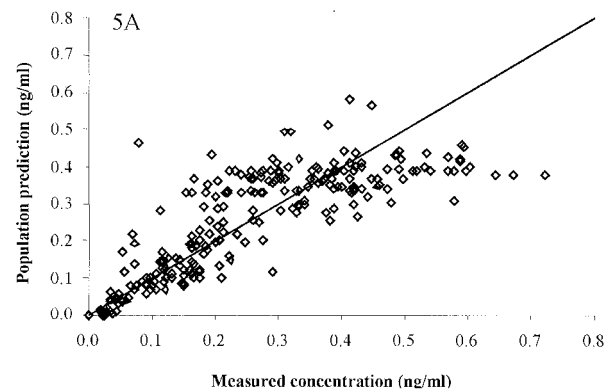

Fig. 5. Correlations between predicted and measured sufentanil concentrations for the population (*A*) and individuals (*B*).

Fig. 4. Negative correlation between median performance error (MDPE) and body mass index (BMI) during sufentanil infusion.

Table 5. Final Estimates for Population Pharmacokinetic Parameters of Sufentanil in Obese Patients

Parameter	Values, CV (%)	95% CI
Pharmacokinetic		
Cl (l/min)	1.27 (23)	1.07 to 3.76
Vc (l)	37.1 (20)	24.0 to 109.8
Q (l/min)	0.87 (44)	0.23 to 2.57
Vp (l)	92.7 (22)	30.6 to 274.4
Residual Variability		
Proportional error (%)	23	
Additive error (ng/ml)	0.016	

Cl = clearance; CV = coefficient of variation for the population parameter estimate; Q = intercompartmental clearance; Vc = central compartment volume of distribution; Vp = peripheral compartment volume of distribution; 95% CI = confidence interval 95%.

minimum alveolar concentration by at least 60% (0.2–0.5 ng/ml).[19] Sufentanil concentrations determined during anesthesia and recovery were similar to sufentanil EC_{50}–EC_{95} concentrations that assure adequate anesthesia and rapid return to consciousness during cardiac surgery or when sufentanil is coadministered with propofol.[18,20,21] In clinical practice, stopping the infusion at pneumoperitoneum exsufflation allows safe ex-

Fig. 6. Correlations between body mass index and clearance (Cl) or central compartment volume of distribution (Vc). BMI = body mass index.

tubation with sufficient residual analgesia during recovery. The times to spontaneous ventilation and tracheal extubation for our patients were similar to those observed when bolus intravenous sufentanil was coadministered with propofol TCI.[22] The plasma sufentanil concentration measured at the beginning of spontaneous ventilation was half that defined by Shafer and Varvel (0.25 ng/ml), being consistent with these events,[21] but assured sufficient residual analgesia during recovery.[23,24]

Although several sufentanil pharmacokinetic models for obese patients receiving bolus injections[14] or for normal-weight patients on TCI have been published,[6,25] it is important to select the proper pharmacokinetic parameters because, should these parameters be strongly biased, a large PE would be expected. Brusset *et al.*[26] showed that blood sampling is required for a long time after sufentanil discontinuation to obtain a precise estimation of the pharmacokinetic parameters. When a low dose of a drug is given, as in TCI, plasma drug concentrations may fall below the limits of detection before the terminal phase. So, the half-life is shortened, the volume of distribution is diminished, and Cl is increased. In some patients, our period of blood sampling was inferior to 24 h. This may explained the difference that we observed in the terminal half-life and Vp with Gepts. Data concerning the use and accuracy of sufentanil administered by TCI are sparse and contradictory, varying with the population studied and the models used. Kern *et al.*[27] examined the performance of a pharmacokinetic model–driven infusion device using the sufentanil parameter sets derived from a pediatric population. Their model was correlated to age and weight, and the predictive accuracy of plasma sufentanil concentrations was good (MDAPE, 32%). Better results with TCI are usually obtained in children, whose pharmacokinetic variabilities might be lower because of the general lack of chronic disease and more narrow weight distribution at any given age when compared with adults.[28]

Bailey *et al.*[20] evaluated the accuracy of sufentanil TCI using the model of Hudson[25] in adults undergoing cardiac surgery. Sufentanil was the only anesthetic agent. Plasma sufentanil concentrations revealed great bias and inaccuracy (MDPE of 116% and MDAPE of 130%) in spite of the strong correlation between measured and predicted concentrations ($r^2 = 0.77$, $P < 0.05$). Very little has been published about sufentanil TCI for noncardiac surgery, and nothing has been published concerning obese patients. Schraag *et al.*[29] studied bias (mean PE) and precision (mean absolute PE) of sufentanil TCI after discontinuation and during recovery, also using the pharmacokinetic variable sets of Hudson. The TCI bias and inaccuracy were −17 and 20.1%, respectively. Thus, the Hudson model slightly overestimated the plasma sufentanil concentration after the infusion had been stopped.

Gepts *et al.*[6] defined another pharmacokinetic parameter set based on their dose-range study. The Gepts
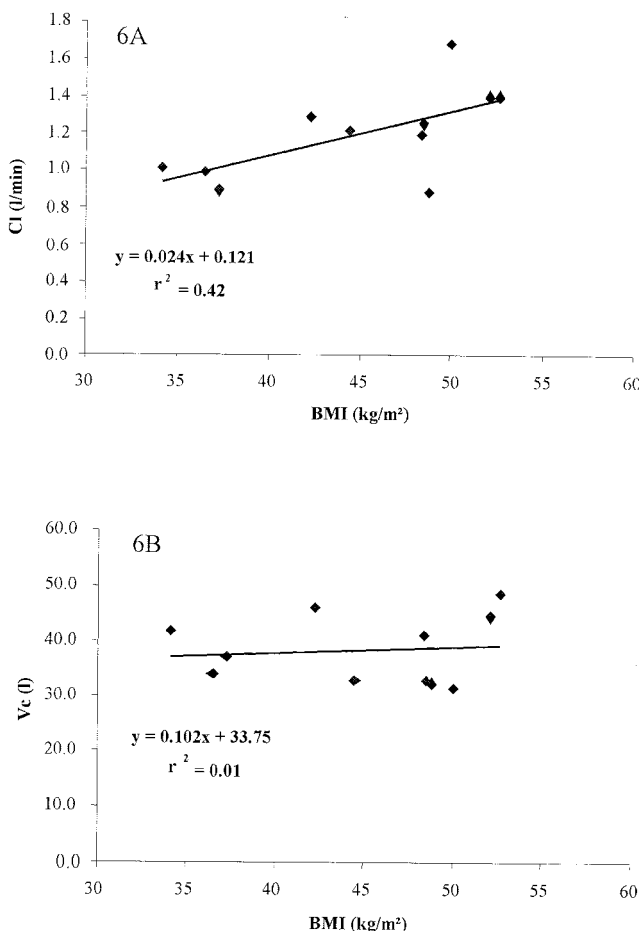
multidose model has several advantages. Arterial blood samples were taken until 48 h after infusion. Sufentanil pharmacokinetics were linear within the dose range studied (250 μg–1,500 μg). However, no relationship with age, weight, or LBM was found for Vc, Vdss, Cl, and elimination half-life. Pandin *et al.*[30] examined the Gepts model during prolonged TCI administration in normal-weight patients. They found that the PE 90th percentile, MDPE, and MDAPE were 35.5, 10, and 20.7%, respectively. Plasma sufentanil TCI concentration range was 0.2–1 ng/ml. Thus, the Gepts model accurately predicted plasma concentrations in lean patients (42–75 kg) with acceptable MDPE, wobble, and divergence, without any major time influence.

Our results confirmed that the Gepts model can also be applied to obese patients. The population pharmacokinetic model with our data gave results similar to those obtained with the Gepts model in terms of pharmacokinetic parameters and accuracy. However, our model's bias was negative, but it was not significantly different from zero. Therefore, based on our model, it is not possible to know if sufentanil concentrations will be under estimated or overestimated. Nevertheless, a linear relationship was found between bias and BMI during sufentanil infusion. For a BMI greater than 40 kg/m^2, Cm was lower than Cp. That finding might be explained by a higher Vd and/or increased clearance as a function of excess body weight. A pharmacokinetic analysis using a population approach was performed to determine whether the estimated parameters were different in our patients and could explain this lower Cm. The two-compartment model was used to investigate whether certain covariates could improve the fit and decrease the interindividual variability. However, none of the demographic parameters tested (particularly weight and BMI) were able to significantly lower the objective function. Clearance tended to increase with BMI, whereas the Vc was independent. Wada *et al.*[31] also observed this relationship between clearance and obesity (Cl: lean = 0.21 l/min, +50% overweight = 0.26 l/min, +100% overweight = 0.29 l/min). This enhanced Cl may be due to increased hepatic blood flow. Because the hepatic extraction ratio of sufentanil is around 0.6–0.8, its Cl relies mainly on hepatic blood flow. These measured results suggest that the concentration predicted by the Gepts model could be overestimated as a consequence of more rapid Cl in obese patients.

In conclusion, the accuracy of the pharmacokinetic parameters described by Gepts *et al.*[6] for sufentanil TCI is sufficient for clinical application in obese patients in combination with propofol. As of 40 kg/m^2, the plasma sufentanil concentration overestimation rises with the increasing BMI.

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Appendix

The following formulas were used for predictive accuracy analysis:

1. Median prediction error: $MDPE_i$ = median $\{PE_{ij}, j = 1, \ldots, N_i\}$, where N_i is the number of PE values obtained for the ith subject.

2. Median absolute prediction error: $MDAPE_i$ = median $\{PE_{ij}, j = 1, \ldots, N_i\}$, where N_i is the number of PE values obtained for the ith subject.

3. The divergence is defined as the slope of the linear regression line of [PE] plotted against time and is expressed in percent per hour. A positive value indicates the progressive widening of the gap between predicted and measured concentrations, whereas a negative value reveals that the measured concentrations converge on the predicted values.

4. In the ith subject, the percent wobble is calculated as follows: $Wobble_i$ = median $\{PE_{ij} - MDPE_i \ j = 1, \ldots, N_i\}$.