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Population Pharmacodynamics and Pharmacokinetics of Remifentanil as a Supplement to Nitrous Oxide Anesthesia for Elective Abdominal Surgery

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Background: **Remifentanil blood concentrations necessary for adequate intraoperative anesthesia have not been defined. The goal of this study was to determine the blood concentrations of remifentanil needed for anesthesia with 66% nitrous oxide during intraabdominal surgery. In addition, the pharmacokinetics of remifentanil and the effects of covariates on both the pharmacodynamics and the pharmacokinetics were determined.**

Methods: **Anesthesia was induced and maintained with 66% nitrous oxide in oxygen and remifentanil. Remifentanil was administered by a computer-controlled infusion pump that rapidly attained, and then maintained, constant remifentanil blood concentrations. If the patient showed signs of inadequate anesthesia (autonomic or somatic response), the target concentration was increased by 1 or 2 ng/ml. If no response occurred during a 15-min period, the concentration was decreased by 1 or 2 ng/ml. Remifentanil pharmacodynamics and pharmacokinetics were estimated using NONMEM.**

Results: **The remifentanil blood concentration for which there is a 50% probability of adequate anesthesia during abdominal surgery (C_{b50}) with 66% nitrous oxide was 4.1 ng/ml in men and 7.5 ng/ml in women. The C_{b50} values for prostatectomy, nephrectomy, and other abdominal procedures were 3.8, 5.6, and 7.5 ng/ml, respectively. Remifentanil pharmacokinetics were best described by a two-compartment model with lean body mass as a significant covariate, where V_1 = 0.129(lean body mass-50) + 3.79 l, V_2 = 6.87 l, CL_1 = 0.0389(lean body mass-50) + 2.34 l/min and CL_2 = 1.14 l/min.**

Conclusions: **The C_{b50} differed according to patient gender. However, because surgery type was not specified for each man or woman, this may reflect a difference in surgical procedure. (Key words: CACI, covariates, gender, NONMEM.)**

DIFFERENT perioperative stimuli need different opioid plasma concentrations to suppress patient clinical response.[1] There is great pharmacodynamic variability among patients undergoing the same type of surgery.[1,2] Knowledge of the opioid concentrations necessary for adequate anesthesia in a particular patient undergoing a specific procedure, together with the knowledge of the pharmacokinetics, may improve the ability of the anesthesiologist to define a more specific dose regimen.

Remifentanil is a new synthetic opioid with an onset of drug effect that is as rapid as alfentanil and a rapid offset of effect because of its ester metabolism in blood and tissues.[3] The blood concentrations of remifentanil necessary to suppress patient response to defined intraoperative stimuli are not known. The pharmacokinetics of remifentanil after a relatively short-duration administration[3–7] have been studied extensively. Minto *et al.*[3] found in healthy volunteers that age and lean body mass (LBM) had a significant effect on pharmacokinetics. However, the pharmacokinetics of remifentanil have not been studied after prolonged surgical administration.

The goals of the current study were first to determine the blood concentration *versus* the anesthetic-effect relation of remifentanil as a supplement to nitrous oxide anesthesia during surgery, using clinically relevant end points (heart rate, blood pressure, movement) as a measure of the drug effect. Second, the pharmacokinetics of remifentanil and the effects of covariates such as surgery type, patient age, gender, weight, and LBM on both the pharmacodynamics and the pharmacokinetics were evaluated during clinical situations. Third, the predictive performance of the pharmacokinetic model of Minto *et*

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‡STANPUMP is available from Steven L. Shafer, M.D., Anesthesiology Service (112A), PAVAMC, 3801 Miranda Avenue, Palo Alto, California 94304.

§Beal SL, Sheiner LB: NONMEM User's Guide. San Francisco, CA, University of California, 1992.

al.[3] was assessed by comparing the predicted remifentanil blood concentration with the actual measured blood concentration.

Methods

After we obtained approval from the Stanford Administrative Panel on Human Subjects in Medical Research, 20 women and 20 men, classified as status 1–3 by the American Society of Anesthesiologists (ASA) and who were 18 yr or older and undergoing elective intraabdominal surgery, were enrolled. Patients were within 35% of ideal body weight and not pregnant or breast feeding. Excluded from the study were patients with symptomatic ischemic heart disease, congestive heart failure, renal or hepatic dysfunction, severe respiratory disease, seizures, or a history of substance abuse. No patient received opioids or benzodiazepines within 9 h or barbiturates within 24 h of the start of the study.

Anesthesia Protocol

Before surgery, a 0.9% normal saline infusion was started and a 300- to 500-ml bolus was administered. Midazolam, in a 1- to 2-mg intravenous dose, was administered before additional lines were inserted. A 20-gauge radial artery catheter was inserted to collect blood samples and for continuous blood pressure measurement. Arterial blood pressure and heart rate were monitored continuously and recorded on magnetic tape. Baseline blood pressure was determined as the lowest observed arterial reading before the start of anesthesia induction.

Pancuronium, in a 0.02-mg/kg intravenous dose, was administered to attenuate muscle rigidity and bradycardia. After the patient breathed 100% oxygen for 3 min, anesthesia was induced with 66% nitrous oxide in oxygen and remifentanil. An infusion pump controlled by a lap-top computer programmed with the software STANPUMP‡ and pharmacokinetic data previously determined in volunteers[3] (table 1) were used to target remifentanil blood concentrations. For induction, the target blood concentration was increased 2 ng/ml every 20 s to reach a target blood concentration of 12 ng/ml in 2 min. The patient was encouraged to continue breathing until loss of consciousness, defined as no response to verbal stimulation or vigorous physical shaking. If the patient did not lose consciousness in 3 min after reaching the target concentration of 12 ng/ml, the remifentanil target concentration was increased 1 or 2 ng/ml every 3 min until loss of consciousness. Succinylcholine, in an intravenous dose of 1 mg/kg, was administered after loss of consciousness, and the lungs were ventilated by bag and mask for 4 min before tracheal intubation. After intubation, the target concentration of remifentanil was reduced to 5 ng/ml. Ventilation was adjusted to maintain an end-tidal carbon dioxide concentration of 35–40 mmHg. To help identify a somatic response, patients were not paralyzed completely (train-of-four $\geq$ 1), and vecuronium was administered only if necessary for surgery. Neuromuscular block was monitored by train-of-four stimulation of the ulnar nerve.

Table 1. Pharmacokinetic Parameters for the Pharmacokinetic Model Used in the Computer-controlled Infusion of Remifentanil

Parameter	Value
Volumes (L)	
Central (V1)	5.1 − 0.0201 · (Age − 40) + 0.072 · (LBM − 55)
Rapid peripheral (V2)	9.82 − 0.0811 · (Age − 40) + 0.108 · (LBM − 55)
Slow peripheral (V3)	5.42
Clearances (L/min)	
Metabolic (Cl1)	2.6−0.0162 · (Age − 40) + 0.0191 · (LBM − 55)
Rapid peripheral (Cl2)	2.05 − 0.0301 · (Age − 40)
Slow peripheral (Cl3)	0.076 − 0.00113 · (Age − 40)

LBM = lean body mass.

If, at any time during surgery, the patient showed signs of inadequate anesthesia, the target concentration of remifentanil was increased by 1 or 2 ng/ml. If necessary, this was repeated every 3 min. Inadequate anesthesia, which is a response to surgical stimuli, was defined by the following criteria:[1]

1. an increase in systolic blood pressure more than 15 mmHg from baseline lasting at least 30 s;
2. a heart rate more than 90 beat/min in the absence of hypovolemia lasting at least 30 s;
3. other autonomic signs, such as sweating, flushing, or lacrimation;
4. somatic responses, such as movements, swallowing, coughing, or grimacing.

If no clinical response, as just defined, occurred during a 15-min period, the target concentration as predicted by STANPUMP was reduced by 1 or 2 ng/ml. Neostigmine, in a dose of 1 mg, and 0.5 mg atropine given intravenously were administered at the completion of skin closure to reverse any residual neuromuscular block. The trachea was extubated after the patient recovered consciousness and when ventilation was adequate with-

out verbal stimulation (frequency, > 8 breaths/min; end-tidal carbon dioxide, < 45 mmHg; tidal volume > 7 ml/kg). If a patient did not regain adequate ventilation within 5 min after discontinuation of nitrous oxide, the remifentanil concentration was decreased by 1 or 2 ng/ml. Pain immediately after extubation was treated with a 1- or 2-ng/ml increase in the remifentanil blood concentration. The postoperative pain regimen was started after tracheal extubation. Patients had a choice of postoperative pain control consisting of patient-controlled analgesia, systemic opioids, or a lumbar epidural catheter. Patients using a patient-controlled analgesia after operation received a 5- or 10-mg intravenous morphine bolus. Patients with epidural catheters received a 10- to 20-ml mixture of lidocaine, 2%, with 1:200,000 epinephrine plus 1 ml 8.4% sodium bicarbonate. Patients were questioned on the day after surgery for perioperative recall.

Remifentanil Blood Sampling and Analysis

Arterial blood samples for measuring remifentanil blood concentrations were collected before induction of anesthesia, immediately before tracheal intubation, at skin incision, at skin closure, at the time of extubation, and 15, 30, and 60 min after extubation. Additional samples were taken before any change in the target remifentanil blood concentration and 5 and 15 min after a target blood concentration was attained. Samples were collected into tubes containing sodium heparin and immediately transferred to tubes containing 50% citric acid (to inactivate esterases) before freezing at −20°C. The remifentanil analyses were performed in our laboratory at Stanford University with high-performance liquid chromatography using ultraviolet detection.[8] Analysis precision was confirmed by cross-validation with the Glaxo Wellcome laboratory that developed the original remifentanil assay.[8] Cross-validation was performed at 3.5, 15, and 160 ng/ml, with coefficients of variation of 9.8%, 3.7%, and 2.8%, respectively.

Data Analysis

Pharmacodynamics. The presence or absence of clinical responses to surgery and corresponding remifentanil blood concentrations were fitted to the following version of the Hill equation.

$$\text{Probability of No Response} = \frac{C_b^{\gamma}}{C_{b50}^{\gamma} + C_b^{\gamma}}$$

where C_b is the measured remifentanil blood concentration, C_{b50} is the blood concentration of remifentanil at which there is a 50% probability of no response, and γ is the slope of the response curve. Initially, a two-stage analysis was performed without covariates. A Laplacian conditional estimation method was applied using NONMEM.§ Thereafter, a generalized additive model[9] was used to identify linear and nonlinear relations between the individual C_{b50} estimates and the covariates, age, American Society of Anesthesiologists status, patient gender, and type of surgery. The type of abdominal surgery was divided into prostatectomy, nephrectomy, and other lower abdominal procedures. Covariates were chosen from the generalized additive model analysis for the next step in the analysis based on improvement in the Akaike's information criteria. These covariates were incorporated in the model and further evaluated with NONMEM. The final pharmacodynamic parameters were estimated with a population mixed-effects modeling approach to give a typical value for the population. A constant coefficient of variation model was used to describe the interindividual variability.

Pharmacokinetics. Blood concentration and time data were analyzed by nonlinear regression using NONMEM. Initially, a naïve pooled and two-stage analysis were performed without covariates to determine the initial estimates of the pharmacokinetic parameters and to determine whether a one-, two-, or three-compartment model best described the patient data. A generalized additive model analysis was performed, as described before, to assess age, American Society of Anesthesiologists status, weight, LBM, gender, height, and body surface area as possible covariates in the pharmacokinetic model. To enable comparison with previous pharmacokinetic analysis of remifentanil,[3] the same formula for body surface area and LBM were used for calculations. Covariates were identified for further analysis in the same manner as described for the pharmacodynamic analysis. Significant covariates from the generalized additive model analysis were incorporated in the pharmacokinetic model, and the final evaluation was performed with NONMEM. Population parameters were estimated with a first-order conditional estimation method and allowed interaction between inter-(η)- and intra-(ϵ)-individual variability. This method enabled assessment of model misspecification because of interindividual variability and provided *post hoc* Bayesian estimates for the individual parameters. The value of η relates the difference in the individual from the "typical" individual. The ϵ is the individual value of the residual error. The value of η has a mean of zero and a variance equal to ω.[2] The value of ω is an estimation of the percentage coefficient

Table 2. Subject Demographics

	Males	Females
Number of patients	20	20
Age (yr) (mean ± SD)	61.6 ± 8.8	48.3 ± 13.6
Age (yr) (range)	46–73	28–78
Weight (kg ± SD)	82.2 ± 11.9	61.4 ± 9.5
LBM (kg ± SD)	61.9 ± 7.6	43.5 ± 4.1

LBM = lean body mass.

of variation (%CV) of the individual parameters. A constant coefficient of variation model was used to describe residual variability in the parameters. The objective function of NONMEM was used to assess improvement in fit, and a probability value was reported based on the likelihood ratio test. The weighted residual (WR) was used to assess the performance of each pharmacokinetic model. The WR was expressed as a percentage and was calculated as follows:

$$WR = \frac{C_m - C_p}{C_p} * 100$$

where C_m is the measured remifentanil blood concentration and C_p is the remifentanil blood concentration predicted by the pharmacokinetic model. The median value of the absolute WR (MDAWR)[10] from the entire data set was calculated for each proposed population model to assess overall accuracy. Bias in the model was described by the median value of the WR.[10] Final assessment of improvement in the pharmacokinetic model was assessed by the objective function of the NONMEM, the median value of the absolute WR, the median value of the WR, and visual assessment of the residual error plots. The residual error plot is the ratio of the measured concentration over the predicted concentration *versus* time.

The predictive performance of the pharmacokinetic data of Minto *et al.*[3] used to program STANPUMP was assessed by the residual error plots and the prediction error (PE). The PE was calculated in the same way that WR was. Accuracy was described by median absolute prediction error and bias by median prediction error.

Results

Patients

Table 2 shows patient demographics. Thirty-four patients lost consciousness at the target remifentanil concentration of 12 ng/ml for induction, 4 lost consciousness at a target remifentanil blood concentration of 14 ng/ml, and the other 2 patients lost consciousness at 16 and 20 ng/ml. Regardless of the gradual increase in remifentanil concentration and pretreatment with pancuronium, 14 patients had mild muscle rigidity, and six patients had moderate to severe muscle rigidity, one of whom was difficult to ventilate by mask. Hypotension (systolic blood pressure < 80 mmHg) occurred in 11 patients during anesthesia induction and was treated successfully with 5 mg intravenous ephedrine and an intravenous fluid bolus. During surgery, one patient had an episode of sinus bradycardia (heart rate < 45 beats/min) that was treated with 0.5 mg atropine. Increasing the remifentanil blood concentration controlled all periods of inadequate anesthesia. After discontinuation of the nitrous oxide, patients responded to commands in a median of 7 min. No patients required naloxone. Thirty-nine of 40 patients were admitted to the postanesthesia care unit after operation, and one patient was admitted to the intensive care unit for surgical reasons. One patient reported recall, described as a pushing or pressure sensation with no pain, without recollection of conversations or other components of the anesthesia or surgery. The patient could not indicate the duration of the recall period but thought it might have occurred at the start or the end of the procedure.

Pharmacodynamic Analysis

The response–no response data of the 40 patients for the single-response events (intubation, skin incision, and skin closure) (fig. 1) could not be fitted by logistic regression. This was a result of the lack of remifentanil concentrations (fig. 1) low enough to result consistently in a response to these stimuli and high enough to consistently prevent a response. Figure 1 shows the remifentanil concentrations at extubation (range, 0.5 to 7.8 ng/ml).

The type and number of clinical responses recorded during intraabdominal surgery are recorded in table 3. In each patient, response–no response data were measured repeatedly during surgery. Figure 2 shows the remifentanil blood concentration *versus* the probability of no response curves obtained by logistic regression for each patient for the intraabdominal component of surgery. The range of C_{b50} was 1.5 to 68.8 ng/ml, with a median of 5.1 ng/ml (table 4). Two patients lacked overlap in the response–no response data (patients 17 and 28, table 4) and could not be included in the population analysis. The C_{b50} values in these patients were estimated as the mean of the highest "response" concentration and the

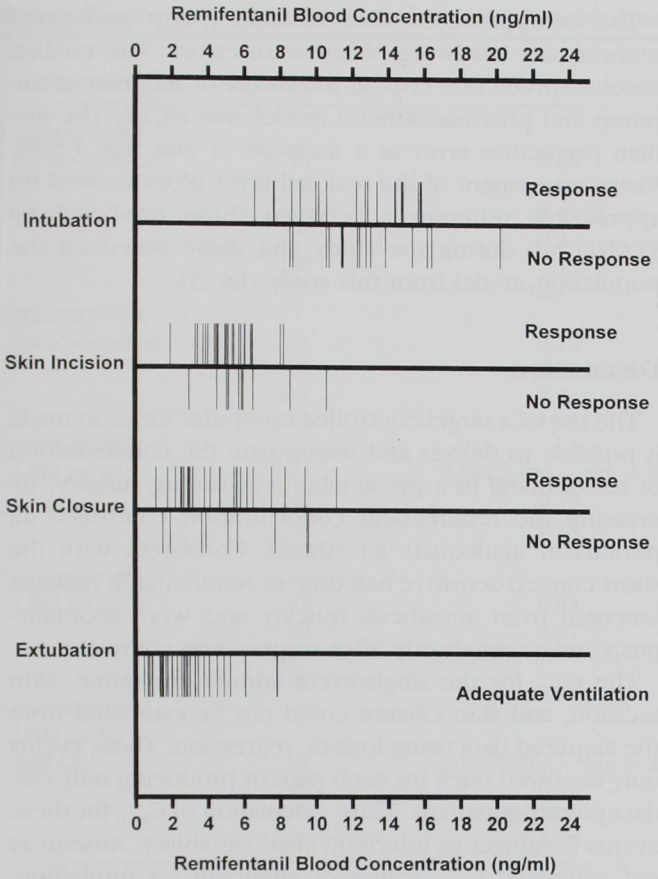

Fig. 1. The remifentanil concentration with the individual response or no response for intubation, skin incision, skin closure, and the remifentanil concentration at extubation with adequate respiration.

lowest "no response" concentration. One of these patients had the highest remifentanil requirement with a C_{b50} of 68.8 ng/ml. In the population model without covariates, the C_{b50} was 5.7 ng/ml. Patient gender and surgery type were significant covariates ($P < 0.001$, table 5). The C_{b50} was 4.1 ng/ml in men and 7.5 ng/ml in women. The C_{b50} values for prostatectomy, nephrectomy, and other abdominal procedures were 3.8, 5.6, and 7.5 ng/ml, respectively. A final analysis incorporating patient gender and surgery type showed no improvement over each covariate alone. Age was not a significant covariate.

Pharmacokinetic Analysis

All 40 patients were included in the pharmacokinetic analysis. The initial two-stage analysis comparing one-, two-, and three-compartment models found that a two-compartment model showed the best fit to the data ($P < 0.001$), with no further statistical improvement from a third compartment. A population analysis was then performed and it also showed that a two-compartment model best represented the data ($P < 0.001$) with no further statistical improvement from a third compartment. The possible covariates, as determined by the generalized additive model analysis, were substituted into the pharmacokinetic model in a stepwise manner. The result of covariate analysis showed an improvement in fit with LBM as a covariate on the clearance of the first compartment. There was no improvement with LBM alone as a covariate on the volume of the first compartment. The best overall model was with the combined effect of the covariate LBM on both the volume and the clearance of the first compartment ($P < 0.005$, table 6). The parameters for the population model were V_1 =

Table 3. Type and Number of Responses during Surgery

Response	Number of Responses
BP	130
HR	12
S	56
D	14
BP + HR	16
BP + S	16
BP + D	6
BP + L	1
HR + S	4
S + D	6
BP + S + D	5
HR + S + D	1
BP + S + D + L	1

BP = systolic arterial pressure 15 mmHg above baseline; HR = heart rate greater than 90 beats/min; S = somatic response; D = diaphoresis; L = lacrimation.

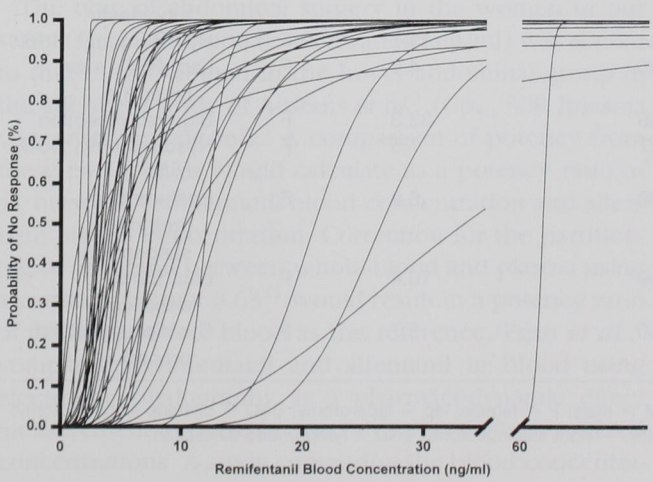

Fig. 2. The remifentanil concentration-effect curves for 40 patients during intraabdominal surgery.

Table 4. Individual Values of C_{b50} for the 40 Subjects

Subject Number	C_{b50} Value	Gender	Surgery
1	12.0	M	Prostatectomy
2	4.0	M	Prostatectomy
3	4.7	M	Prostatectomy
4	3.0	M	Nephrectomy
5	3.4	M	Prostatectomy
6	5.2	M	Nephrectomy
7	3.3	M	Prostatectomy
8	10.7	M	Cystectomy
9	7.5	M	Prostatectomy
10	4.7	M	Prostatectomy
11	6.7	M	Prostatectomy
12	3.7	M	Prostatectomy
13	3.1	M	Prostatectomy
14	4.4	M	Prostatectomy
15	1.5	M	Prostatectomy
16	5.5	M	Prostatectomy
17	2.3	M	Prostatectomy
18	2.4	M	Prostatectomy
19	8.8	M	Prostatectomy
20	10.2	F	Lap, tumor debulking
21	1.7	M	Prostatectomy
22	12.3	F	Lap, hysterectomy
23	3.1	F	Lap, hysterectomy
24	1.8	F	Urethrolysis
25	2.9	F	Colectomy, hysterectomy, BSO
26	20.0	F	Hysterectomy, BSO
27	5.7	F	Ureteral implant
28	68.8	F	Cholecystectomy
29	3.8	F	Lap, myomectomy
30	5.3	F	Hysterectomy
31	4.2	F	Myomectomy, tuboplasty
32	26.5	F	Hysterectomy, BSO, Burch procedure
33	2.9	F	Myomectomy, tuboplasty
34	13.1	F	Hysterectomy, BSO
35	4.9	F	Lap, RSO, mass resection
36	33.3	F	Sigmoid resection
37	7.5	F	Hysterectomy, BSO, LND
38	6.9	F	Hysterectomy, urethral suspension
39	10.4	F	Lap, tumor debulking
40	5.7	F	Cystoplasty, Burch procedure

M = male; F = female; lap = laparotomy; BSO = bilateral salpingectomy; RBO = right salpingectomy; LND = lymph node dissection.

$0.129 \cdot (\text{LBM} - 50) + 3.79$ l, $V_2 = 6.87$ l, $CL_1 = 0.0389 \cdot (\text{LBM} - 50) + 2.34$ l/min and $CL_2 = 1.14$ l/min.

The computer-controlled infusion pump performed without any hardware or software errors. The median absolute prediction error as a measure of accuracy of the pump and pharmacokinetic model was 18.2%. The median prediction error as a measure of bias was 1.59%. Visual assessment of the residual error plots showed no appreciable differences between those predicted by STANPUMP during the study and those based on the population model from this study (fig. 3).

Discussion

The use of a target-controlled computer infusion made it possible to deliver and manipulate the concentration of remifentanil in a predictable way during surgery. Increasing the remifentanil concentration controlled all periods of inadequate anesthesia. Consistent with the short context-sensitive half-time of remifentanil, patients emerged from anesthesia quickly and were spontaneously breathing shortly after surgery was complete.

The C_{b50} for the single-event stimuli intubation, skin incision, and skin closure could not be estimated from the acquired data using logistic regression. These events only occurred once for each patient producing only one data point per patient. Thus, calculation of C_{b50} for these events is subject to interindividual variability. Ausems *et al.*[1] estimated C_{p50} values of alfentanil for intubation, skin incision, and skin closures. The inability to estimate these values for remifentanil does not suggest a difference in interindividual variability between alfentanil and remifentanil but is more a reflection of different study designs. In our study, the target remifentanil blood concentrations were chosen to approximate the estimated value of C_{b50} for intubation, skin incision, and closure. The excellent performance of the model of Minto *et al.*[3] resulted in blood concentrations that were close to the target concentration. As a result, our method did not

Table 5. Covariates and C_{b50} Values from the Pharmacodynamic Analysis

Covariate	C_{b50} (ng/ml)	Objective Function	% CV
None	5.7	843	61.8
Gender			
Male	4.1	806	56.9
Female	7.5		
Surgery type			
Prostatectomy	3.8	805	61.5
Nephrectomy	5.6		
Other abdominal	7.5		

CV = coefficient of variation.

Table 6. Pharmacokinetic Models Considered and Associated Statistics

PK Model	Parameter	Value	% CV	Objective Function	MDAWR	MDWR
3 compartment, no covariables	V1	3.88	58.8	1498.1	9.4	1.41
	V2	6.62	38.7			
	V3	0.0192	70.9			
	Cl1	2.4	22.7			
	Cl2	1.15	42.1			
	Cl3	13.7	13.7			
2 compartment, no covariables	V1	3.79	58.9	1497.9	9.56	1.52
	V2	6.39	41.1			
	Cl1	2.4	22.8			
	Cl2	1.21	31.1			
2 compartment LBM on V1	V1	0.124*(LBM − 50) + 4.33	20.5	1492.3	9.45	1.32
	V2	6.76	38.5			
	Cl1	2.4	22.6			
	Cl2	1.08	48.6			
2 compartment, LBM on CL1	V1	3.83	58.5	1467.6	9.71	1.89
	V2	6.41	40			
	Cl1	0.0378*(LBM − 50) + 2.34	15.3			
	Cl2	1.21	30.2			
2 compartment, LBM on V1 and CL1	V1	0.128*(LBM − 50) + 3.79	47.3	1459.3	9.65	1.51
	V2	6.87	31.9			
	Cl1	0.0389*(LBM − 50) + 2.34	15.1			
	Cl2	1.14	48.2			

Volumes are expressed in liters and clearances in liters/min. NONMEM's post hoc step was included during the estimation of these parameters.

PK = pharmacokinetic; CV = coefficient of variation; MDAWR = median absolute weighted residual; MDWR = median weighted residual; LBM = lean body mass; V = volume; Cl = clearance.

result in remifentanil concentrations high enough to consistently prevent a patient response or low enough to consistently result in a patient response. In contrast, the method of Ausems *et al.*[1] resulted in plasma concentrations below which a response was always observed and above which a response was never observed. Ausems *et al.*[1] did not target plasma concentrations with a computer-controlled infusion pump but rather used a bolus and zero-order infusion dosing scheme that resulted in less accurate control of the alfentanil target concentration.

The C_{b50} values estimated for the intraabdominal part of the surgery exhibited considerable interindividual variability, which is similar to published results for alfentanil.[1] In the current study, one female patient had a very high C_{b50} value of 68.8 ng/ml. The only apparent reason for the increased remifentanil requirements was the long-term use of benzodiazepines for insomnia. This same patient had exhibited opioid tolerance approximately 1 yr previously while in an intensive care unit. At that time, her breathing was assisted by mechanical ventilation, and she was administered a prolonged infusion of fentanyl for sedation.

The type of abdominal surgery in the women in our study (C_{b50} 7.5 [blood concentration] ng/ml) was similar to that in the women in the lower abdominal group in the alfentanil study of Ausems *et al.*[1] (Cp_{50} 309 [plasma concentration] ng/ml).[1] A comparison of potency from these two studies would calculate as a potency ratio of 41 between remifentanil blood concentration and alfentanil plasma concentration. Correction for the partitioning of alfentanil between whole blood and plasma using a partition ratio of 0.63[11] would result in a potency ratio of 26 using whole blood as the reference. Egan *et al.*,[4] comparing remifentanil and alfentanil in blood using electroencephalography as a pharmacodynamic effect measurement, reported a potency ratio of 19 using blood concentrations. A study comparing the blood concentrations of remifentanil and alfentanil needed to produce loss of consciousness found a potency ratio of 20.[12]

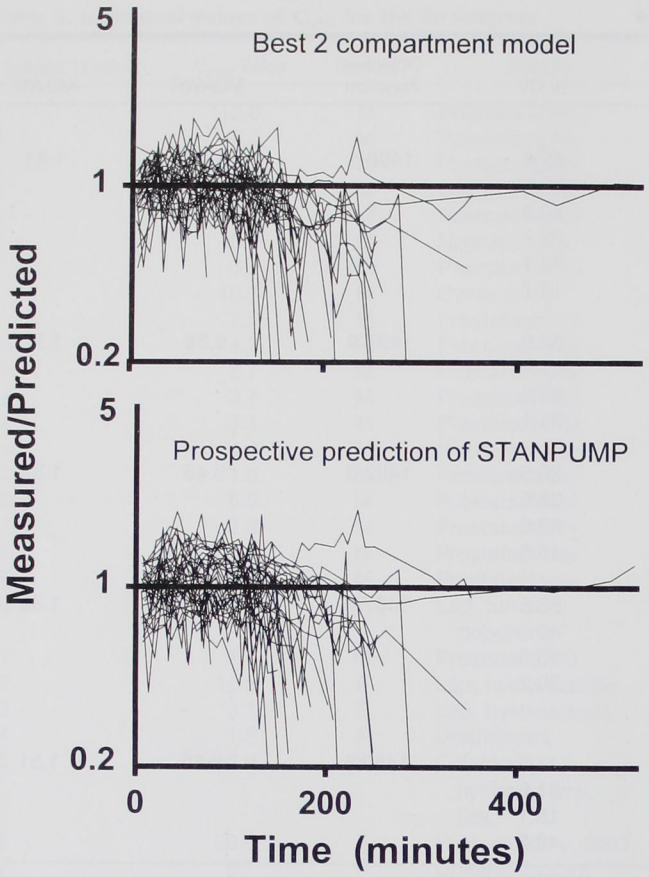

Fig. 3. The y axis displays the ratio of measured to predicted remifentanil concentrations for all 40 patients. The line drawn at y = 1 represents perfect prediction. The top panel shows the best two-compartment model based on the population parameters without the NONMEM *post hoc* estimation step. The bottom panel was generated from predictions of the previously determined three-compartment model used in programming the infusion pump.

The pharmacodynamic model was improved with patient gender as a covariate, but it was unclear whether this was a result of the different types of abdominal surgery that the men and women underwent. A similar improvement in the pharmacodynamic model could be obtained with the type of surgery, but this was divided according to patient gender because most of the male patients underwent prostate surgery. It may be possible that different types of abdominal surgery necessitate different remifentanil concentrations to suppress inadequate anesthesia. A further possibility is that a gender difference may exist. The data from the current study cannot determine which covariate, gender or surgery type, is truly the cause of this pharmacodynamic difference. Future studies would be necessary to assess the effect of gender on anesthetic requirements.

Age of the patients had no effect on the pharmacodynamics. The effect of age on pharmacodynamics has been debated previously.[3] There continues to be a discrepancy between studies with clinical end points and studies with electroencephalographic end points.[1,3,13–15] This may indicate that the pharmacodynamic mechanism and the modulation of the mechanism underlying these two different opioid effects may not be identical. As Minto *et al.*[3] noted, one of the limitations of our study design is the low resolution of clinical end points. This lower resolution will make it difficult to detect an effect of covariates such as age. Minto *et al.*[3] suggest that implementation of age in their pharmacodynamic model resulted in a relatively small improvement in the prediction of the electroencephalographic effect. Therefore, it may not be surprising that our study did not detect an age effect on the pharmacodynamics. However, the suppression of the response to noxious stimuli (which the C_{b50} in the current study reflects) truly may not be affected by age.

The pharmacokinetic parameters derived from the current study were best described using a two-compartment model with LBM as a significant covariate on V_1 and Cl_1. Remifentanil was best described by a three-compartment model in a previous study using volunteers.[3] One reason for the lack of a third compartment in the current study may be attributed to the study design determined by the clinical situation and also by the lack of low remifentanil blood concentrations. The infusion was altered in a predetermined way depending on the response of the patient. The remifentanil concentration already was low when the infusion was discontinued, and the concentration quickly fell below the detection limit of the assay, making determination of the third compartment difficult. The lack of a third compartment in this clinical situation would suggest that the third compartment is not clinically significant. The study by Minto *et al.*[3] used a higher remifentanil infusion rate than that normally necessary for clinical practice. A remifentanil pharmacokinetic study investigating the effect of temperature and cardiopulmonary bypass also found that the pharmacokinetics were described sufficiently by a two-compartment model.[16]

In conclusion, the population C_{b50} value of remifentanil for the intraabdominal part of surgery was 5.7 ng/ml. There was a gender difference in the C_{b50}, with a C_{b50} in men of 4.1 ng/ml and 7.5 ng/ml in women, but it remains unclear whether gender or type of abdominal surgery is the true cause of this difference. When type of surgery is considered, the C_{b50} values for prostatectomy, nephrectomy, and other abdominal procedures are 3.8,

5.6, and 7.5 ng/ml, respectively. There was a large interindividual variability in the C_{b50} value, and consequently, there is a large overlap among the different groups. The pharmacokinetic parameters derived from the current study were best fit with a two-compartment model, with LBM as a significant covariate on V_1 and Cl_1, and they are in the same range as previously reported in volunteers.[3,4] The use of published pharmacokinetic parameters of remifentanil for computer-controlled administration is an accurate method for drug delivery during surgery.

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