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Pharmacokinetics of Remifentanil (GI87084B) and Its Major Metabolite (GI90291) in Patients Undergoing Elective Inpatient Surgery

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Background: **Remifentanil is a highly potent opioid with a rapid onset and a short duration of action due to its rapid hydrolysis by esterases in blood and tissues. The major metabolite of remifentanil, GI90291, is much less potent than remifentanil.**

Methods: **The pharmacokinetics of remifentanil and its major metabolite, GI90291, were determined in 24 patients undergoing elective inpatient surgery. Remifentanil was administered as a 1-min infusion (2, 5, 15, and 30 μg/kg) after the induction of anesthesia and tracheal intubation. Serial arterial blood samples were collected over 6 h and assayed for remifentanil and GI90291.**

Results: **The pharmacokinetics of remifentanil were described using a three-compartment model. Total clearance (250–300 l/h) of remifentanil was independent of dose and was approximately three to four times greater than the normal hepatic blood flow. Volume of distribution at steady state (25–40 l) also was independent of dose. The terminal half-life of remifentanil ranged from 10 to 21 min. Covariate analysis of remifentanil clearance and patient demographics showed that patient body weight, age, and gender did not influence total clearance. This suggests that remifentanil may not need to be dosed according to body weight in adult patients. A simulation was conducted to determine the time required for a 50% reduction in effect site concentration after an infusion designed to maintain a constant effect site concentration. The time required for a 50% reduction in the effect site concentration of remifentanil (3.65 min) was considerably less than that for sufentanil (33.9 min), alfentanil (58.5 min), and fentanyl (262 min). The pharmacokinetics of the major metabolite, GI90291, were independent of the dose of remifentanil. The mean terminal half-life of GI90291 ranged from 88 to 137 min.**

Conclusions: **The pharmacokinetics of remifentanil are consistent with its rapid elimination by blood and tissue esterases; its major metabolite is eliminated more slowly but is not likely to make any significant contribution to the total effect because of its much lower potency. The rapid onset and short duration of action of remifentanil make it well suited for titration of dose (infusion rate) to the desired degree of effect. (Key words: Analgesics: remifentanil. Anesthetics, intravenous: remifentanil. Pharmacokinetics: computer simulation; population; remifentanil.)**

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THE use of opioids as adjuncts to general anesthesia has the risk of postanesthetic ventilatory depression. In the past, the duration of ventilatory depression has been related to accumulation of the opioid, which generally is related directly to the dose and duration of opioid administration.

Remifentanil (hydrochloride salt of 3-[4-methoxycarbonyl-4-[(1-oxopropyl) phenylamino]-1-piperidine]propanoic acid, methyl ester; GI87084B; fig. 1) is a novel synthetic μ-opioid agonist that possesses potent analgesic activity.[1] An ester linkage in the chemical structure of remifentanil renders this compound susceptible to rapid metabolism by blood and tissue esterases.[1] The primary metabolic pathway of remifentanil is de-esterification to form a carboxylic acid metabolite (GI90291), which has only $^1/_{300}$–$^1/_{1,000}$ the

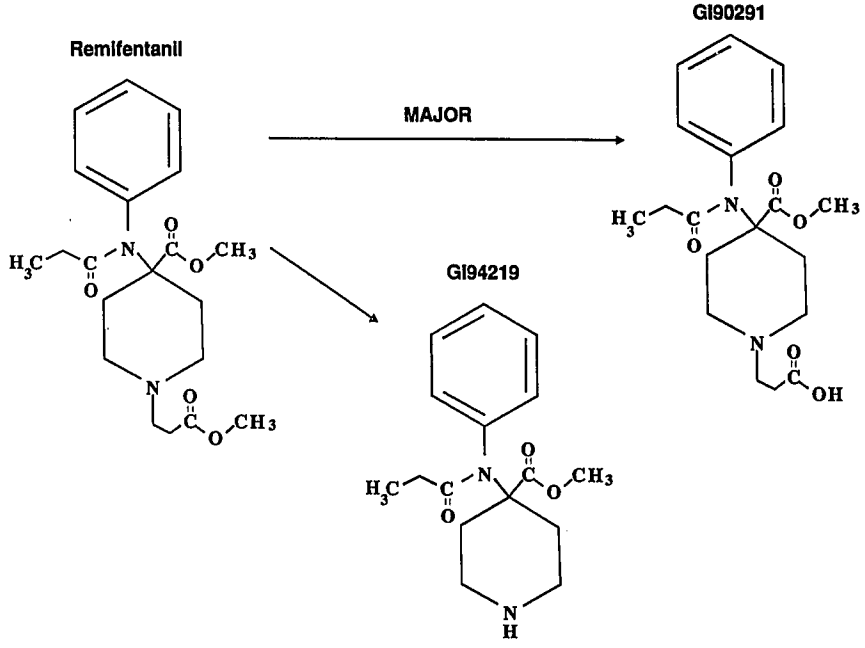

Fig. 1. Chemical structure and proposed metabolic pathways of remifentanil (GI87084).

potency of the parent compound in animal models.‖ N-dealkylation of remifentanil (GI94219) is a minor metabolic pathway in humans.‖ Remifentanil has a rapid onset and offset of action and rapid blood-brain equilibration, properties that facilitate titration of dose according to effect.[2] This combination of pharmacokinetic and pharmacodynamic properties of remifentanil make it attractive for use in general anesthesia.

This study was designed to investigate the pharmacokinetics of remifentanil at clinically relevant doses[3] in anesthetized patients undergoing elective inpatient surgery. The doses of remifentanil ranged from 2 to 30 μg/kg. Infusion simulations were conducted to gain an understanding of the relationship between the pharmacokinetic parameters and duration of the desired pharmacologic effect.

Methods and Materials

Dosage Preparation

Remifentanil hydrochloride (Glaxo, Research Triangle Park, NC) was supplied in single vials as a lyophilized powder containing 1 mg of the free base. The drug in each vial was reconstituted with 1 ml of sterile water for injection. The appropriate volume, based on patient weight, was withdrawn and diluted to a final volume of 15 ml with 5% dextrose in water. Each patient received an infusion volume of 6 ml over 1 min delivered by a Baxter infusion pump (model AS20GH, Baxter Diagnostics, McGaw Park, IL).

Study Design

This was an open-label, escalating-dose, pharmacokinetic study in 24 patients undergoing elective inpatient surgery. The study protocol was approved by the Emory University Human Investigations Committee. Each patient included in the study had normal clinical laboratory test results (serum chemistry, hematology, and routine urinalysis), 12-lead electrocardiogram, physical examination, and medical history, and gave written informed consent. Patients were reevaluated at 24–36 h postinfusion (clinical laboratory tests, adverse events, 12-lead electrocardiogram, and physical examination). None experienced any adverse event from anesthesia and none had any surgical complication.

Patients received 10 mg metoclopramide and 150 mg ranitidine orally 1–2 h before induction of anesthesia and 1–2 mg intravenous midazolam just before induction. Anesthesia was induced with etomidate (0.3–0.5 mg/kg). A radial arterial catheter was inserted

‖ Glaxo Inc: Unpublished data.

for continuous monitoring of blood pressure and for sampling of blood for remifentanil and GI90291 assays. After administration of vecuronium (0.1 mg/kg) to facilitate tracheal intubation, the lungs were ventilated with 66% N_2O in oxygen to maintain an end-tidal carbon dioxide pressure of 29–36 mmHg. Anesthesia was supplemented with isoflurane as needed. Glycopyrrolate (up to 0.5 mg intravenously) was administered before remifentanil infusion. During the course of anesthesia, all 24 patients received an antibiotic intravenously. Near the end of the operation or in the recovery room, 19 patients received an opioid (none of which interfered with the remifentanil assay), 1 patient received ketorolac, and 3 patients received lidocaine intravenously. In addition, local infiltration with bupivacaine was done in 11 of the 24 patients. Neostigmine and additional glycopyrrolate were administered to 15 of the 24 patients to antagonize the residual effects of vecuronium at the end of the operation; blood sampling for remifentanil assay was completed in all but one patient before neostigmine administration.#

Twenty-four patients were assigned to four groups, each containing six patients (three men and three women). Remifentanil (2, 5, 15, and 30 μg/kg) in a total volume of 6 ml was infused at a constant rate over 1 min at approximately 10 min after tracheal intubation. Clinical data from each dose group were reviewed before dose escalation in subsequent groups.

Arterial blood samples (5 ml) were collected into a heparinized syringe before the infusion, at the end of the infusion, and at 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 15, 20, 25, 30, 40, 60, 90, 120, 180, 240, and 360 min after the infusion for determination of remifentanil and GI90291 concentrations in whole blood. Aliquots of the blood were denatured immediately by the addition of two volumes of acetonitrile containing internal standards (deuterated remifentanil and deuterated GI90291) and promptly extracted into four volumes of methylene chloride. The organic and aqueous phases were separated and stored at −70° C until analysis.

Analytical Methodology

Remifentanil concentrations were determined by gas chromatography-high-resolution mass spectrometry-selected ion monitoring.** The lower and upper limits of quantitation for remifentanil were 0.1 ng/ml and 250 ng/ml, respectively, and the interday coefficient of variation for the assay was less than 11.5%. GI90291 concentrations were determined using gas chromatography-mass spectrometry.[4] The lower and upper limits of quantitation for GI90291 were 0.05 ng/ml and 100 ng/ml, respectively, and the interday coefficient of variation was less than 13.2%.

Pharmacokinetic Analysis

The pharmacokinetics of remifentanil were determined using nonlinear least squares regression (PCNONLIN 4.0, SCI Software, Lexington, KY). Two- and three-compartment models with intravenous infusion were assessed for goodness of fit. Model selection was based on F ratio test, visual inspection of residual plots, and the predicted and observed concentration-time profiles for each patient.[5] Data were weighted as either C^{-1} or C^{-2}, where C is the observed blood concentration of remifentanil.

The area under the zero and the first moment of the concentration-time curves of remifentanil were determined using the coefficients and exponents obtained from the nonlinear regression analysis. Total clearance, volume of distribution in the central compartment, volume of distribution at steady state, and mean residence time were determined by standard methods.[6] Total clearance and volume of distribution at steady state were compared among dose groups by standard linear regression techniques (PC SAS, version 6.04, SAS Institute, Cary, NC). For GI90291, the area under the concentration-time curve was determined using the trapezoidal rule and extrapolated to infinity (AUC_{inf}) using the rate constant (k_{em}) describing the terminal log-linear phase. The maximum blood concentration (C_{max}) and time to maximum blood concentration (T_{max}) for GI90291 were determined by visual inspection of the blood concentration-time data for each patient. The terminal half-life ($t_{½}$) of GI90291 was obtained from $\ln 2/k_{em}$. To assess the linearity of GI90291 pharmacokinetic parameters with dose of remifentanil, the AUC_{inf} and C_{max} were normalized using the corre-

Studies at Glaxo Inc. have shown that remifentanil hydrolysis is not dependent on cholinesterases and is not altered *in vitro* by the presence of cholinesterase inhibitors.

** Grosse CM, Davis IM, Arrendale R, Jersey J, Amin J: Determination of GI87084 in human blood by liquid-liquid extraction and GC/HRMS/SIM using a deuterated internal standard (abstract). Fourth International Symposium on Pharmaceutical and Biomedical Analysis, Baltimore, Maryland, April 18–21, 1993.

Table 1. Patient Demographics

	Remifentanil Dose (μg/kg)			
	2	5	15	30
Age (yr)				
Male*	42.3 (6.4)	39.0 (14.7)	22.3 (3.8)	52.0 (8.0)
Female*	42.3 (6.7)	37.3 (1.2)	40.7 (6.1)	39.7 (10.8)
Weight (kg)				
Male*	98.6 (9.0)	91.3 (7.5)	81.7 (9.8)	92.6 (12.4)
Female*	63.6 (7.7)	67.1 (12.9)	71.6 (7.0)	67.7 (15.5)
Height (cm)				
Male*	98.6 (9.0)	91.3 (7.5)	81.7 (9.8)	92.6 (12.4)
Female*	63.6 (7.7)	67.1 (12.9)	71.6 (7.0)	67.7 (15.5)
ASA Physical Status				
1	4	2	3	3
2	2	4	3	1
3	0	0	0	2
Duration of surgery (min)†	131.3 (31.9) 94–172	169.5 (67.7) 77–266	178.8 (68.0) 108–265	179.7 (114.8) 49–317
Surgery				
Oral	0	2	0	1
Upper abdominal	1	0	0	0
Lower abdominal	4	2	3	2
Urologic	0	1	0	2
Extremity	1	1	3	1

Values are mean (SD in parentheses); n = 6 for each dose group.

* n = 3.

† Mean (SD in parentheses) and range.

sponding dose of remifentanil before regression analysis.

NONMEM Analysis

Correlation of demographic factors with pharmacokinetic parameters was conducted using a nonlinear mixed effects modeling technique (NONMEM).†† The effect of body weight, age, and gender on remifentanil clearance were evaluated.

Infusion Simulations

Using an infusion simulation,[7,8] the time for the concentration of remifentanil to decrease by 50% in the hypothetical effect compartment after an infusion designed to maintain a constant effect site concentration was determined for infusion durations up to 240 min. This parameter has been referred to as a context sensitive half-time and, in some cases, is believed to be a more informative parameter than terminal elimination half-life.[9] The simulation procedure required input of micro rate constants (*i.e.*, k_{12}, k_{21}, k_{13}, k_{31}, k_{10}), which were determined from the compartmental analysis of the data obtained in this study, and the effect site equilibration rate constant (k_{e0}), which was obtained from a previous study with remifentanil.[2] For comparison, the simulation also was performed by us for other opioids (alfentanil, sufentanil, and fentanyl) using pharmacokinetic parameters obtained from the literature.[7]

Results

A summary of the demographic characteristics and surgery conditions for the male and female patients in each dose group is provided in table 1. Twenty-two of the 24 patients were categorized as ASA physical status 1 or 2. Patient age and weight ranged from 18 to 60 yr and 50 to 109 kg, respectively. At the 24-h follow-up assessment, no clinically relevant changes were

†† Beal SL, Sheiner LB: NONMEM User's Guide. San Francisco, University of California San Francisco, 1989.

Table 2. Pharmacokinetic Parameters after a 1-min Infusion of Remifentanil in 24 Patients

Parameter	Dose (μg/kg)			
	2	5	15	30
$t_{1/2}\ \pi$ (min)*	0.42 (0.08)	0.48 (0.15)	0.53 (0.14)	0.54 (0.20)
$t_{1/2}\ \alpha$ (min)*	1.96 (0.75)	2.79 (0.98)	3.08 (0.78)	3.69 (1.80)
$t_{1/2}\ \beta$ (min)*	10.19 (4.71)	14.35 (7.79)	15.67 (6.31)	20.47 (13.03)
VD_{ss} (l)	24.31 (11.50)	35.97 (22.26)	27.98 (5.30)	39.75 (23.66)
Clearance (l/hr)	246.6 (52.6)	283.5 (99.0)	279.4 (97.5)	296.8 (75.2)

Values are mean (SD in parentheses); n = 6 for each dose group.

VD_{ss} = volume of distribution at steady state.

* Harmonic mean (jackknife standard deviation) (see reference 10).

noted in the clinical laboratory tests, electrocardiogram, or physical examination.

Remifentanil Pharmacokinetics

The concentration-time profile of remifentanil was best described by a triexponential function in all but four patients, whose concentration-time profiles could be described adequately by a biexponential function. For consistency, the pharmacokinetics for these four patients also are described using a three-compartment model (table 2). Inspection of residual plots and the observed and predicted concentration-time curves indicated that a weighting of C^{-2} was optimal for all patients. Figure 2 shows the observed and predicted blood concentration-time profile of remifentanil for a patient who received the 30 μg/kg dose.

The mean (±SD) observed concentrations for the four doses are displayed in figure 3 and the mean (±SD) pharmacokinetic parameters for each dose group are

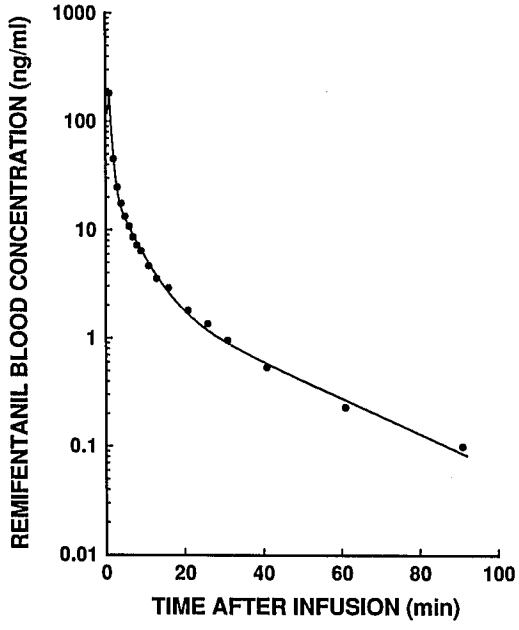

Fig. 2. Observed (dots) and predicted (line) remifentanil blood concentration time profiles for patient 20, who received 30 μg/kg remifentanil.

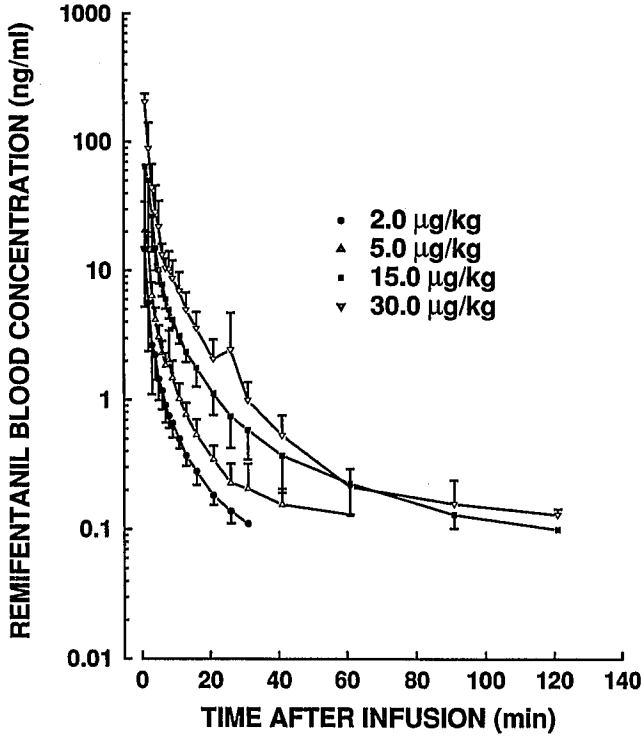

Fig. 3. Mean (±SD) blood concentration-time curves after a 1-min infusion of remifentanil at doses of 2 (●), 5 (△), 15 (■), and 30 μg/kg (▽). n = 6 for each dose.

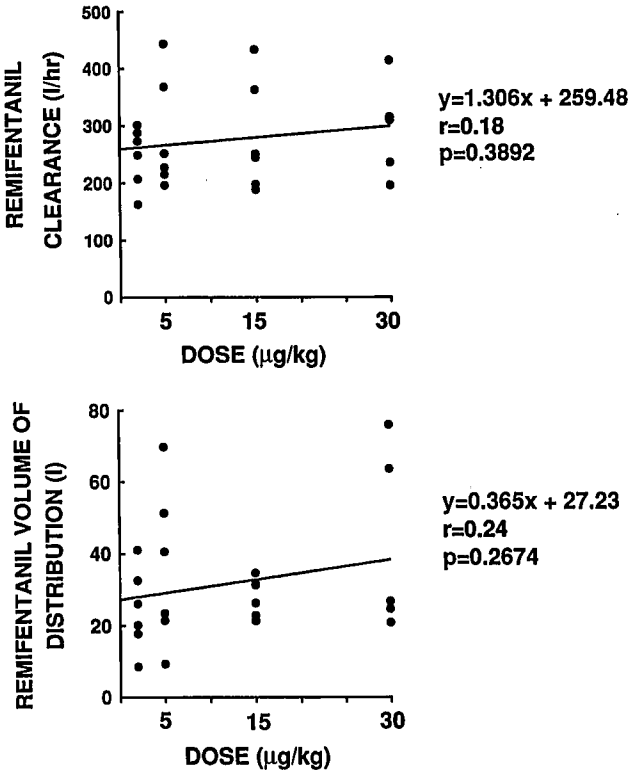

Fig. 4. Regression analysis plots of remifentanil clearance (Cl; *top*) and volume of distribution at steady state (Vd_{ss}; *bottom*) *versus* dose of remifentanil.

listed in table 2. A complete list of the pharmacokinetic parameters for each patient is provided in the appendix. Among the four dose groups, the half-life (harmonic mean[10]) for each of the three disposition phases ($t_{1/2}\pi$, $t_{1/2}\alpha$, $t_{1/2}\beta$) ranged from 0.42 to 0.54 min, 2.0 to 3.7 min, and 10.2 to 20.5 min, respectively. Mean residence time (5.7–7.7 min) was relatively consistent among the dose groups. Total clearance was independent of the dose of remifentanil (P = 0.3892; fig. 4, top) with means ranging from 247 ± 53 l/h in the 2 μg/kg group to 297 ± 75 l/h in the 30 μg/kg group. Mean volume of distribution at steady state ranged from 24.3 ± 11.5 l in the 2 μg/kg group to 39.8 ± 23.7 l in the 30 μg/kg group and also was independent (P = 0.2674; fig. 4, bottom) of the dose of remifentanil. Volume of distribution in the central compartment ranged from 5.7 to 8.0 l and accounted for approximately 20% of the total distribution volume.

NONMEM Analysis

A three-compartment linear pharmacokinetic model was assumed for the NONMEM analysis. The covariates (age, body weight, and gender) were evaluated against individual clearance values (not corrected for body weight). There was no evidence of a relationship between remifentanil clearance and body weight, age, or gender in this population of anesthetized patients. The population average estimate of clearance (240 l/h) obtained from the NONMEM analysis was consistent with that obtained from the individual compartmental analysis.

GI90291 Pharmacokinetics

The pharmacokinetic parameters of the metabolite, GI90291, are listed in table 3, and the mean concentration-time plots of GI90291 are shown for the four remifentanil doses in figure 5. Regression analysis indicated that the dose-normalized AUC_{inf} (P = 0.5597; fig. 6, top) and dose-normalized C_{max} (P = 0.6821; fig. 6, bottom) were constant in the dose range studied (*i.e.*, linear pharmacokinetics). T_{max} was reached at ap-

Table 3. Pharmacokinetic Parameters for GI90291 after a 1-min Infusion of Remifentanil in 24 Patients

Parameter	Remifentanil Dose (μg/kg)			
	2	5	15	30
T_{max} (min)	34 (16)	26 (6)	29 (7)	31 (10)
C_{max} (ng/ml)	3.02 (0.54)	6.68 (1.52)	20.7 (3.6)	41.5 (9.1)
AUC_{inf} (ng · min · ml^{-1})	456.6 (64.1)	807.1 (131.3)	2,609.2 (258.4)	5,698.8 (1,663.8)
Terminal $t_{\frac{1}{2}}$ (min)	137.4 (55.9)	128.0 (34.0)	88.1 (10.1)	99.2 (27.7)
AUC ratio*	15.96 (8.97)	12.35 (2.51)	12.13 (3.04)	11.36 (5.03)

Values are mean (SD in parentheses); n = 6 for each dose group.

* AUC ratio determined by dividing GI90291 AUC_{inf} by remifentanil AUC_{inf}.

T_{max} = time to maximum blood concentration; C_{max} = maximum blood concentration; AUC_{inf} = area under the blood concentration time curve extrapolated to infinity.

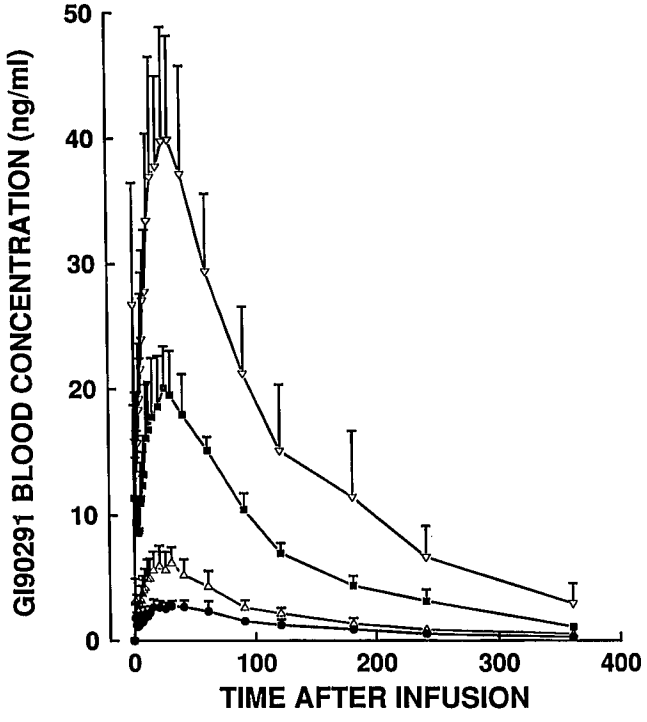

Fig. 5. Mean (±SD) blood concentration-time curves of the metabolite GI90291 after remifentanil doses of 2 (●), 5 (△), 15 (■), and 30 μg/kg (▽). n = 6 for each dose.

proximately 30 min in all dose groups, and the mean terminal $t_{½}$ ranged from 88.1 to 137.4 min. The mean AUC_{inf} ratio (GI90291:remifentanil) was approximately 12:1, indicating that steady-state concentrations of GI90291 would be, on average, approximately 12 times the steady-state concentrations of remifentanil.

Infusion Simulations

The time required for a 50% reduction in the effect site concentration of remifentanil after an infusion designed to maintain a constant effect site concentration[7] was determined using the mean of the micro rate constants for all patients and graphically compared with other opioids (fig. 7, top). Approximately 3.65 min was required for the effect site concentration of remifentanil to decrease by 50%, whereas for sufentanil, alfentanil, and fentanyl, the times required for a 50% reduction in effect site concentration after an infusion for 240 min were 33.9 min, 58.5 min, and 262.5 min, respectively. A plateau in the time required for a 50% reduction in effect site concentration was reached rapidly for remifentanil; however, no apparent plateau in this value was reached for the other opioids for infusion durations of up to 240 min.

The mean of the micro rate constants for each of the four remifentanil dose groups also was used to simulate the times required for a 50% reduction in effect site concentration after an infusion designed to maintain a constant effect site concentration. For infusion durations ranging from 0 to 240 min, the time for a 50% reduction in effect site concentration was similar among the doses (fig. 7, bottom).

Discussion

This study characterized the pharmacokinetics of remifentanil in patients undergoing elective inpatient surgery. The doses selected were based on the range of single intravenous doses relevant to clinical practice[3] and resulted in peak concentrations of up to 200 ng/ml (30 μg/kg).

The pharmacokinetics of remifentanil were best described using a three-compartment model. Since remifentanil is believed to undergo hydrolysis in both blood and tissues,[1] the classic three-compartment model with elimination exclusively from the central (sampled) compartment may be conceptually imprecise for describing the pharmacokinetics of remifentanil. However, if only blood concentrations are measured, a three-compartment model with input into the central compartment and exit rate constants (*e.g.*, k_{10}, k_{20}, k_{30}) associated with two or more of the peripheral compartments is mathematically indistinguishable from a three-compartment model with elimination only from the central compartment (*i.e.*, k_{10}).[6,11] Thus, the analysis is mathematically correct and permits useful and valid extrapolations (*e.g.*, infusion simulations) to be performed.

Previous pharmacokinetic studies have described the disposition of remifentanil using a two-compartment model.[2,12] A three-compartment model was used to characterize the disposition of remifentanil in this study. The difference may relate to the higher dose, longer sampling period, and more frequent sample collection in the present study, leading to higher resolution analysis of the disposition profile. The three-compartment characteristics were not as readily apparent at the lower doses, although the mean concentration-time profiles for the four doses were essentially parallel (fig. 3). The concentration-time profile after

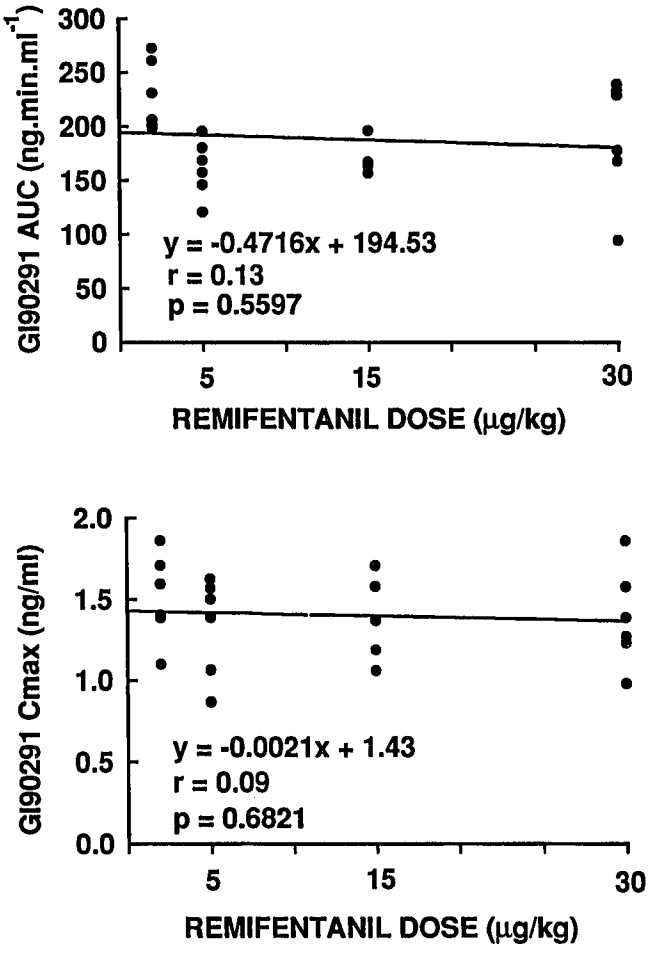

Fig. 6. Regression analysis plot of the area under the concentration-time curve (AUC; *top*) and maximum blood concentration (C_{max}; *bottom*) of the metabolite GI90291 *versus* dose of remifentanil. AUC and C_{max} values for all dose groups were normalized to a dose of 1 μg/kg by dividing the values by the corresponding dose of remifentanil.

the infusion of smaller doses of remifentanil may appear biexponential because blood concentrations reached the lower limit of sensitivity of the assay relatively early in the terminal phase.

The clearance of remifentanil (250–300 l/h) was approximately three- to fourfold greater than the average hepatic blood flow (80 l/h), which is consistent with rapid extrahepatic hydrolysis by blood and tissue esterases. Regression analysis indicated that the clearance of remifentanil was independent of dose, at least within the dose range investigated in this study. This is further supported by the relatively constant area under the concentration-time curve ratios (table 3) for GI90291 and remifentanil (11.36–15.96) among the four dose groups. The volume of distribution of remifentanil (25–40 l) also was independent of dose and indicative of extensive extravascular distribution.

A previous pharmacokinetic/pharmacodynamic study in six healthy male volunteers receiving a 20-min infusion of remifentanil (1–4 $\mu g \cdot kg^{-1} \cdot min^{-1}$) indicated that the systemic clearance and volume of distribution at steady state were 174 l/h and 24 l, respectively.[2]

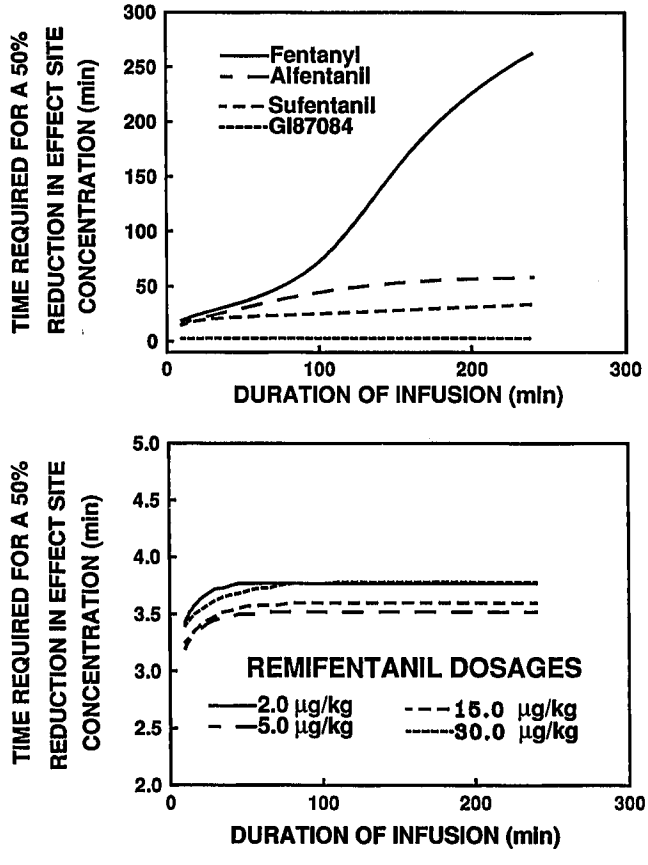

Fig. 7. (*Top*) Simulation of the time required for a 50% reduction in the effect site concentration of remifentanil, sufentanil, alfentanil, and fentanyl after an infusion (duration 0–240 min) designed to maintain a constant effect site concentration. Simulation data for remifentanil were derived from the mean of the micro rate constants for all remifentanil dose groups. Note that all of these opioids have been demonstrated to have dose-independent pharmacokinetics. (*Bottom*) Simulation of the time required for a 50% reduction in the effect site concentration after an infusion (duration 0–240 min) designed to maintain a constant effect site concentration. Simulation data derived from the mean of the micro rate constants for each remifentanil dose group (2, 5, 15, and 30 μg/kg).

The higher clearance of remifentanil in the present study may result from the conditions of general anesthesia and surgery, which differ from those in healthy volunteers.

The population analysis of remifentanil clearance *versus* age, body weight, and gender demonstrated no significant correlation with any of these covariates. The most striking finding, perhaps, was the lack of a relationship between clearance and patient body weight. The clearance of remifentanil was assumed, *a priori,* to be weight-related (*i.e.*, μg/kg), and the study doses were designed with this in mind. The lack of a relationship between clearance and body weight suggests that dosing of remifentanil may not need to be based on body weight, at least in adults within the body weight range studied. Further investigations will be required to confirm this observation.

The initial distribution of remifentanil was extremely rapid, with a half-life ($t_{1/2}\pi$) of approximately 0.5 min, followed by an intermediate disposition half-life ($t_{1/2}\alpha$) of 2–4 min. The mean terminal half-life ($t_{1/2}\beta$) increased from approximately 10 min in the 2 μg/kg group to 20 min in the 30 μg/kg group. This increase is probably a reflection of better characterization of the terminal phase in the higher dose groups and not due to nonlinearities in the pharmacokinetics of remifentanil. Using the average of the macro constants (P, π, A, α, B, β) from all patients, a simulation of blood concentrations showed that, during a constant-rate infusion, 50% and 90% of steady-state concentrations were reached in approximately 1.3 min and 17 min, respectively.

The terminal elimination half-life of a drug may be a poor indicator of duration of pharmacologic effect.[7,8] Relative to total clearance, extravascular distribution may account for a significant portion of the decline in drug concentrations and, consequently, the decline in concentration at the site of action. Comparison of terminal elimination half-life between drugs (*e.g.*, a series of opioids) as a measure of duration of effect, therefore, may be misleading as a predictor of duration of effect. Depending on the dose and duration of infusion, one compound may have a shorter duration of effect compared to a similar compound yet have a longer terminal elimination half-life. We therefore used the data from this study to simulate the time for the concentration of remifentanil in the hypothetical effect compartment to decline by 50% after an infusion designed to maintain a constant effect site concentration. Assuming that a 50% decrease in the effect site concentration relates to a clinically relevant change in opioid effect, the simulations allow a comparison between other opioids (fentanyl, sufentanil, and alfentanil).[7]

The simulation profiles of the times required for a 50% decrease in effect site concentration of remifentanil after an infusion designed to maintain a constant effect site concentration were similar when derived from the data of each of the four remifentanil dose groups (fig. 7, bottom). Similarly, the simulations (fig. 7, top) showed that the time for a 50% reduction in effect site concentration for remifentanil (3.65 min) was considerably less than that for sufentanil (33.9 min), alfentanil (58.5 min), and fentanyl (262 min). Furthermore, a plateau in the time required for a 50% decrease relative to the duration of infusion (fig. 7, top) was reached rapidly for remifentanil but not for the other opioids.

GI90291 is the major metabolite of remifentanil and is eliminated primarily in the urine.‖ The pharmacokinetics of GI90291 were described using noncompartmental methods. The disposition of GI90291 was independent of the dose of remifentanil. AUC_{inf} and C_{max} were proportional to the dose of remifentanil, and T_{max} was similar across dose groups. The mean terminal $t_{1/2}$ of GI90291 was longer than that for remifentanil and ranged approximately from 88 to 137 min. With its low opioid potency relative to remifentanil (1:300–1,000),‖ the metabolite probably contributes very little to the effects of remifentanil.

In summary, the volume of distribution at steady state and total clearance of remifentanil are independent of dose in adult patients undergoing elective surgery. Rapid elimination was observed after high intravenous doses of remifentanil, and the predicted time for a 50% reduction in effect site concentration after an infusion designed to maintain a constant effect site concentration was similar among the four dose groups and considerably shorter than other available opioids. A rapid offset of action combined with a rapid onset of action are characteristics that facilitate the titration of drug dose (*e.g.*, infusion rate) according to each patient's needs. Based on pharmacokinetic and pharmacodynamic characteristics,[2] remifentanil appears to be a promising new opioid for use in anesthesia.

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Appendix

Table A1. Pharmacokinetic Parameters for Individual Patients

Dose (μg/kg)	Parameter	Patient Number 1	2	3	4	5	6
2	Volume	42.44	50.07	93.61	85.73	47.32	69.71
	k21	0.6023	0.7383	0.6240	0.3049	0.3433	0.4345
	k31	0.1426	0.0973	0.1566	0.0417	0.0472	0.0777
	k10	1.0719	0.7604	0.7690	0.9639	0.7785	0.7714
	k12	0.4150	0.5681	0.1097	0.6795	0.2282	0.3252
	k13	0.2378	0.1864	0.4725	0.2286	0.1097	0.2521
	P	40.91	30.21	18.84	21.71	38.15	25.27
	A	4.98	8.68	1.37	1.44	3.79	2.78
	B	1.24	1.05	1.15	0.19	0.32	0.64
	$t_{\frac{1}{2}}\pi$	0.36	0.37	0.47	0.35	0.57	0.46
	$t_{\frac{1}{2}}\alpha$	1.63	1.79	1.25	3.71	2.72	2.24
	$t_{\frac{1}{2}}\beta$	6.20	9.26	7.60	21.08	16.97	12.30
	AUC	43.97	52.54	27.78	24.20	54.29	37.19
	AUMC	160.45	273.72	151.47	218.56	296.66	267.62
		7	8	9	10	11	12
5	Volume	22.43	111.97	73.80	178.43	85.92	28.83
	k21	0.4228	0.2354	0.2895	0.3549	0.3935	0.5016
	k31	0.06678	0.0157	0.0470	0.0852	0.0387	0.1039
	k10	1.4718	0.5830	0.7916	0.4926	0.5374	1.0398
	k12	0.3892	0.2712	0.5719	0.2518	0.3134	0.3432
	k13	0.1516	0.1348	0.1034	0.1459	0.1316	0.2026
	P	210.36	40.81	61.65	23.21	47.72	61.90
	A	11.60	3.64	5.55	3.65	9.71	6.27
	B	0.99	0.20	0.55	1.16	0.77	1.19
	$t_{\frac{1}{2}}\pi$	0.33	0.65	0.43	0.67	0.60	0.40
	$t_{\frac{1}{2}}\alpha$	2.12	4.34	4.17	2.96	2.96	1.88
	$t_{\frac{1}{2}}\beta$	11.55	54.93	17.07	11.27	22.79	8.20
	AUC	151.48	76.60	85.60	56.89	108.30	66.70

	AUMC	447.81	1411.85	559.64	438.97	1069.99	248.16
		13	14	15	16	17	18
15	Volume	89.82	109.67	41.40	110.13	80.70	73.26
	k21	0.3778	0.4131	0.1969	0.3509	0.3273	0.3149
	k31	0.0761	0.0854	0.0370	0.0594	0.0241	0.0407
	k10	0.6045	0.7074	1.0107	0.8629	0.5348	0.7380
	k12	0.2276	0.2216	0.2923	0.7523	0.1606	0.3303
	k13	0.1745	0.1583	0.1622	0.0814	0.0864	0.0814
	P	143.64	118.58	349.73	124.55	158.16	186.79
	A	18.84	15.08	10.77	13.25	26.61	20.82
	B	4.53	3.11	1.81	1.13	1.10	1.25
	$t_{\frac{1}{2}}\pi$	0.61	0.57	0.46	0.37	0.79	0.55
	$t_{\frac{1}{2}}\alpha$	2.56	2.28	4.48	3.83	2.97	3.35
	$t_{\frac{1}{2}}\beta$	12.24	10.27	22.04	13.06	33.70	19.12
	AUC	276.26	193.35	358.49	161.00	347.58	283.01
	AUMC	1807.02	965.12	2457.83	889.58	3322.35	1578.93
		19	20	21	22	23	24
30	Volume	94.18	87.68	100.28	99.81	90.88	78.20
	k21	0.2743	0.3151	0.2730	0.1715	0.2022	0.5051
	K31	0.0492	0.0455	0.0144	0.0372	0.0100	0.0811
	k10	0.7527	0.8963	0.8692	0.3757	0.5371	0.7819
	k12	0.4005	0.5286	0.6682	0.1052	0.2175	0.3129
	k13	0.0673	0.1565	0.0883	0.0296	0.0448	0.1727
	P	295.07	314.30	277.81	269.15	301.99	325.61
	A	27.67	25.21	22.89	30.66	29.84	53.28
	B	2.16	2.68	0.46	2.75	0.47	7.32
	$t_{\frac{1}{2}}\pi$	0.52	0.41	0.40	1.24	0.80	0.48
	$t_{\frac{1}{2}}\alpha$	4.03	3.49	4.62	5.50	5.09	2.02
	$t_{\frac{1}{2}}\beta$	15.62	18.25	53.25	20.36	75.11	10.75
	AUC	431.67	381.76	346.47	805.39	618.71	493.93
	AUMC	2232.70	2643.06	3859.89	5181.34	7564.99	2399.58

Volume (ml/kg) = volume of central compartment; k21, k31, k12, k13 (min^{-1}) = rate constants describing tranfer of drug between compartments; k10 (min^{-1}) = rate constant describing irreversible elimination of drug; P, A, B (ng/ml) = zero-time intercepts for intravenous bolus (obtained from postinfusion coefficients); $t_{\frac{1}{2}}\pi$, $t_{\frac{1}{2}}\alpha$, $t_{\frac{1}{2}}\beta$ (min) = half lives of respective disposition phase; AUC ($ng \cdot min \cdot ml^{-1}$) = area under the concentration–time curve; AUMC ($ng \cdot min^2 \cdot ml^{-1}$) = area under the first-moment curve.