

Anesthesiology
83:968-975, 1995
© 1995 American Society of Anesthesiologists, Inc.
Lippincott-Raven Publishers

Measured Context-sensitive Half-times of Remifentanyl and Alfentanil

Atul Kapila, M.B., B.S.,* Peter S. A. Glass, M.B., Ch.B.,† James R. Jacobs, Ph.D.,‡ Keith T. Muir, Ph.D.,§ David J. Hermann, Pharm.D.,|| Masa Shiraiishi, M.D.,* Scott Howell, M.D.,# Richard L. Smith, Ph.D.**

Background: The context-sensitive half-time, rather than the terminal elimination half-life, has been proposed as a more clinically relevant measure of decreasing drug concentration after a constant infusion of a given duration. The context-sensitive half-time is derived from computer modelling using known pharmacokinetic parameters. The modelled context-sensitive half-time for a 3-h infusion of alfentanil is 50–55 min and is 3 min for remifentanyl. The terminal elimination half-life is 111 min for alfentanil and 12–30 min for remifentanyl. It has not been tested whether the modelled context-sensitive half-time reflects the true time for a 50% decrease in drug concentration or drug effect.

Methods: Thirty volunteers received a 3-h infusion of remifentanyl or alfentanil at equieffective concentrations. Depression of minute ventilation to 7.5% ET_{CO_2} was used as a measure of drug effect. Minute ventilation response was measured, and blood samples for drug concentration were taken during and after drug infusion. The recovery of minute ventilation (drug effect) and decrease in blood drug concentration was plotted, and the time for a 50% change was determined.

* Visiting Associate, Department of Anesthesia, Duke University Medical Center.

† Associate Professor of Anesthesia, Department of Anesthesia, Duke University Medical Center.

‡ Assistant Professor in Anesthesiology, Department of Anesthesia, Duke University Medical Center.

§ Associate Director of Clinical Pharmacokinetics, Glaxo Inc. Research Institute.

|| Clinical Pharmacokineticist, Glaxo Inc. Research Institute.

Research Fellow, Department of Anesthesia, Duke University Medical Center.

** Assistant Professor, Biometry Division, Department of Community and Family Medicine, Duke University Medical Center.

Received from the Department of Anesthesia, Duke University Medical Center, Durham, North Carolina, and Glaxo Inc. Research Institute, Research Triangle Park, Durham, North Carolina. Submitted for publication November 16, 1994. Accepted for publication July 17, 1995. Supported in part by a grant received from Glaxo Inc. Presented in part at the annual meeting of the American Society of Anesthesiologists, Washington, D.C., October 1993.

Address correspondence to Dr. Glass: P.O. Box 3094, Department of Anesthesia, Duke University Medical Center, Durham, North Carolina 27710. Address electronic mail to: Glass003@mc.duke.edu.

Results: The measured pharmacokinetic context-sensitive half-time for remifentanyl after a 3-h infusion was 3.2 ± 0.9 min, and its pharmacodynamic offset was 5.4 ± 1.8 min. Alfentanil's measured pharmacokinetic context-sensitive half-time was 47.3 ± 12 min, and its pharmacodynamic offset was 54.0 ± 48 min. The terminal elimination half-life modelled from the volunteers was 11.8 ± 5.1 min for remifentanyl and 76.5 ± 12.6 min for alfentanil.

Conclusions: The measured context-sensitive half-times were in close agreement with the context-sensitive half-times previously modelled for these drugs. The results of this study confirm the value of the context-sensitive half-time in describing drug offset compared to the terminal elimination half-life. (Key words: Computer modelling. Opioids: alfentanil; remifentanyl. Pharmacokinetics.)

SEVERAL intravenous drugs have become available for continuous infusion to provide the components of anesthesia. Traditionally, the terminal elimination half-life has been used as a measure of offset of drug action. However, with drugs whose pharmacokinetics can be described by multicompartment models, this is not satisfactory.^{1,2} The context-sensitive half-time, the time to halving of the blood concentration after termination of drug administration by an infusion designed to maintain a constant concentration, has been proposed as a more useful measure of the pharmacokinetic offset of intravenous anesthetics.² By incorporating the effect compartment, the context-sensitive half-time of the pharmacodynamic effect can be modelled.¹ This concept has clinically relevant implications for the administration of intravenous anesthetics in that it would allow a more accurate prediction of the recovery from intravenous infusions at the termination of surgery. However, the concept of context-sensitive half-time has been based on computer modelling and has not been tested *in vivo*.

Remifentanyl is a new anilidopiperidine opioid that contains an ester linkage rendering it susceptible to metabolism by plasma and tissue esterases, which in turn confers it with pharmacokinetics that produce evanescent blood concentrations.³⁻⁵ The terminal

MEASURED CONTEXT-SENSITIVE HALF-TIME

Table 1. Pharmacokinetic Parameters Utilized in CACI

Pharmacokinetic Parameter	Alfentanil	Remifentanil
k10 (/min)	0.0894	0.376
k12 (/min)	0.6540	0.3090
k21 (/min)	0.2090	0.1920
k13 (/min)	0.1180	NA
k31 (/min)	0.0177	NA
V1	2.19 L	0.12 L/kg

CACI = computer-assisted continuous infusion; NA = not applicable.

elimination half-life of remifentanil has been reported as 12–30 min.^{3–5} Alfentanil has a terminal elimination half-life of 111 min.⁶ Computer modelling has predicted a context-sensitive half-time of 3 min for remifentanil³ and 50–55 min for alfentanil¹ after a 3-h infusion.

The aim of this study was to measure the context-sensitive half-time of both remifentanil and alfentanil, in terms of their pharmacokinetic and pharmacodynamic offset. This was done after the administration of these drugs for 3 h by infusion and assessed by the changes in the measured drug concentrations and minute ventilation after termination of the infusions.

Methods

After approval from the Duke University institutional review board for human studies and obtaining written informed consent, 30 paid volunteers were recruited and randomized to receive an infusion of either alfentanil ($n = 15$) or remifentanil ($n = 15$). Inclusion criteria were healthy ASA physical status 1 males, aged 18 to 40 yr, within 20% of ideal body weight. All subjects underwent a medical history and physical examination. Blood samples for hematology and blood chemistries, a urine sample for chemistry and screening for drugs of abuse, and a 12-lead electrocardiogram were obtained. Exclusion criteria were a history of alcohol or drug abuse; smoking more than 10 cigarettes per day; a positive urine screen for drugs of abuse; abnormal renal, hepatic, or hematologic function as assessed by blood a history of opioid use; or anesthesia within 8 weeks of screening and use of prescription medications within 1 week of drug administration. Subjects were not allowed oral intake for 6 h before drug administration, and were instructed to abstain from beverages

containing caffeine or alcohol for 12 h and from tobacco products for 4 h before the initiation of the study.

On the morning of the study, subjects had catheters inserted into a radial artery and a peripheral vein. A nasal cannula, electrocardiograph pads, and a pulse oximeter finger probe were placed. Arterial blood pressure, end-tidal carbon dioxide, respiratory rate, finger peripheral hemoglobin oxygen saturation, electrocardiograph (lead II), and heart rate were continuously monitored and recorded *via* the monitors' RS232 port to a computer-based data acquisition system.

The subjects were randomized double-blind, double-dummy to receive either remifentanil or alfentanil. Blinding was achieved by having the hospital pharmacy prepare two infusion bags, one labelled as remifentanil and the other as alfentanil. For each subject, one bag contained active drug and the other bag contained normal saline. After baseline measurements, both bags were attached to a computer-controlled continuous infusion device⁷ and administered as though each contained active drug. The target blood concentration for remifentanil was 1 ng/ml and for alfentanil was 40 ng/ml. These concentrations were estimated to be equivalent using effect compartment modelling from a previous study.³ The pharmacokinetic model parameters used in the computer-controlled continuous infusion device for this study are listed in table 1.

Minute ventilation at steady-state end-tidal 7.5% CO₂ measured using a bag in a box system⁸ for 5 min was used as a measure of drug effect. The initial 4 min of each minute ventilation run allowed time for equilibration of the inspired carbon dioxide and the respiratory center in the brain. The minute ventilation data reported is the minute ventilation measured in the last

Table 2. The Adjustment in the Target Concentration Made to Obtain a 40–70% Decrease from Baseline of Minute Ventilation When Breathing 7.5% CO₂

% Decrease in Minute Ventilation	Target Serum Concentration Multiplied by
0–20	2.0
21–30	1.5
31–39	1.25
40–70	No change
71–80	0.75
81–90	0.5
>91	0.25

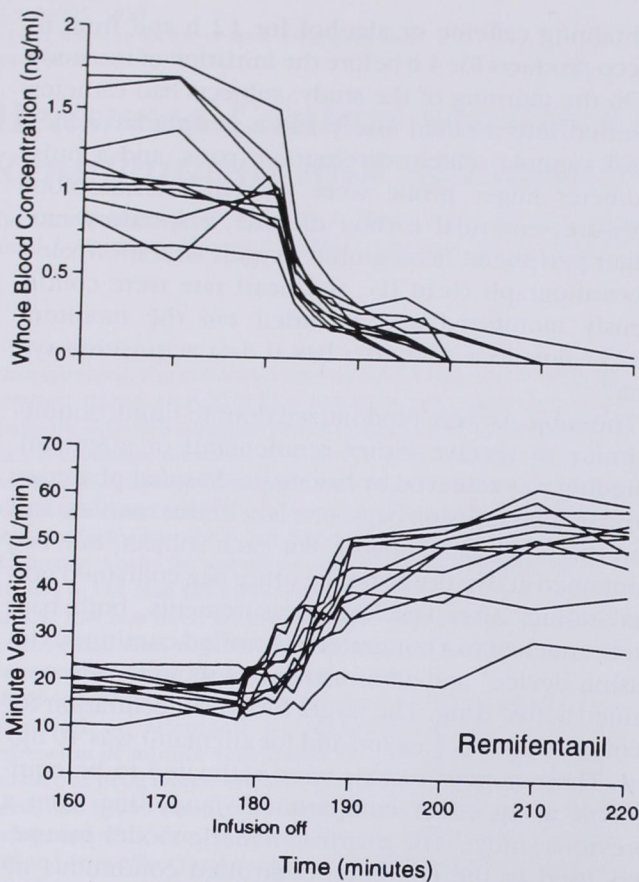


Fig. 1. The upper graph is the decrease in remifentanyl whole blood concentration of each subject after a 3-h infusion adjusted to maintain a 40–70% decrease in minute ventilation when breathing 7.5% CO₂. The lower graph is the recovery of minute ventilation after termination of the same infusion.

(5th) minute. Minute ventilation was evaluated at baseline and every 15 min after the beginning of the drug infusion and until successive measurements were within 40–70% of the subjects' baseline minute ventilation and within 20% of each other. Thereafter, minute ventilation was measured every 30 min and at 170 min. If the minute ventilation depression was outside the desired range, the target concentration of both drugs were simultaneously adjusted as listed in table 2. Subjects requiring more than two adjustments in the target concentration of the opioid within the first 60 min of the infusion were withdrawn from the study.

From 2 min before terminating the infusion until 10 min after the end of the infusion, the bag-in-a-box system was used, and the average minute ventilation for each minute was obtained. This provided minute ven-

tilation measurements for each minute for the first 10 min after termination of drug infusion. Thereafter, minute ventilation measurements (as previously described) were made at 20 and 30 min and every 15 min thereafter until values returned to baseline. Arterial blood (5 ml) was collected at baseline, at multiple times during the infusion and at 1, 3, 5, 7, 10, 15, 20, 30, 45, 60, and 90 min and 2, 3, 4, 5, and 6 h after termination of the infusion. These were immediately processed for subsequent analysis of remifentanyl and alfentanil whole blood concentrations, as previously described using gas chromatography/mass spectrometry with selected ion monitoring.³

The pharmacokinetic offset in whole blood drug concentration was calculated as the percentage decrease in blood drug concentration after the termination of the infusion: % decrease in drug concentration

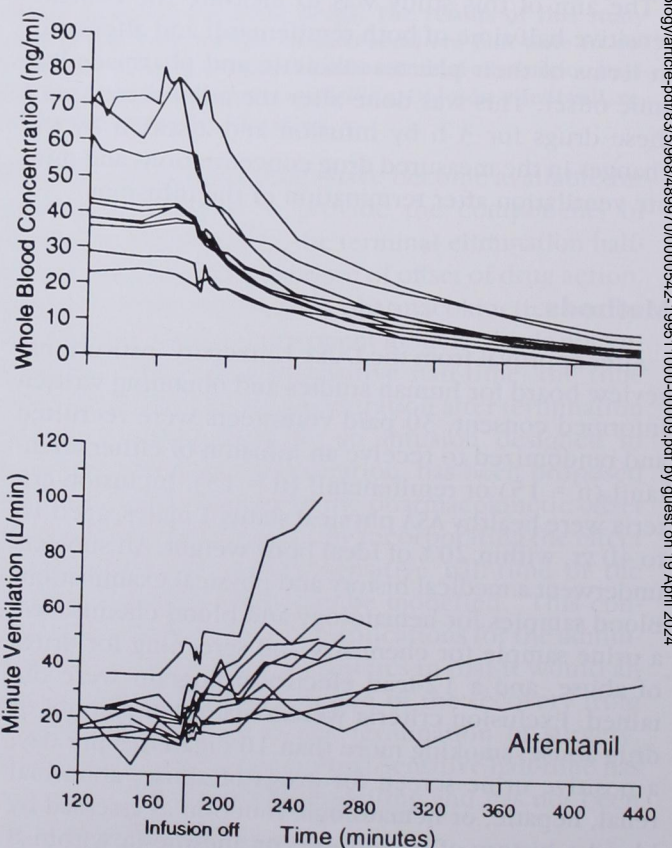


Fig. 2. The upper graph is the decrease in alfentanil whole blood concentration of each subject after a 3-h infusion adjusted to maintain a 40–70% decrease in minute ventilation when breathing 7.5% CO₂. The lower graph is the recovery of minute ventilation after termination of the same infusion.

MEASURED CONTEXT-SENSITIVE HALF-TIME

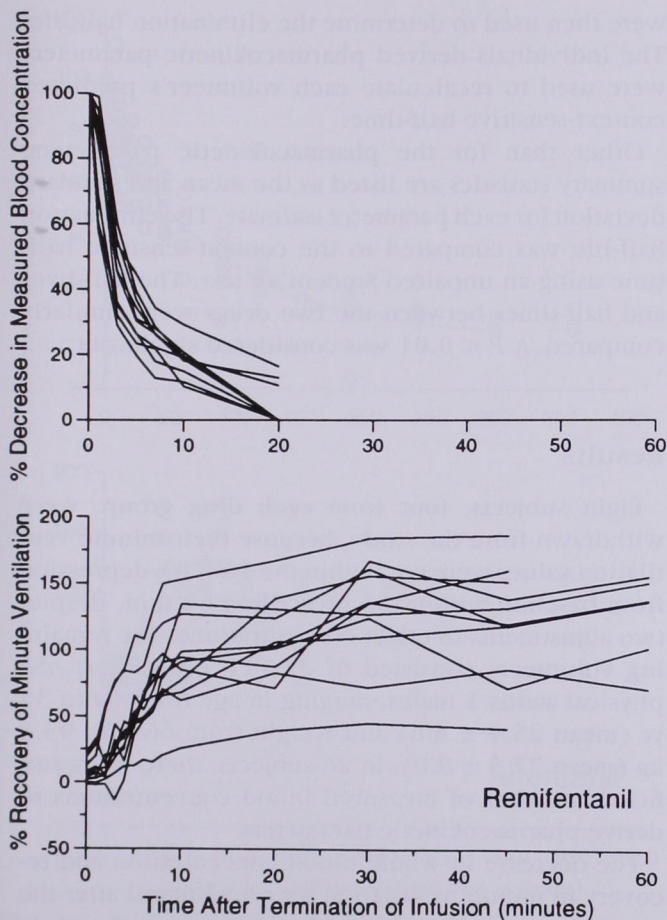


Fig. 3. The upper graph is the percentage decrease in remifentanyl whole blood concentration of each subject after a 3-h infusion adjusted to maintain a 40–70% decrease in minute ventilation when breathing 7.5% CO₂. The lower graph is the percentage recovery of minute ventilation toward the predrug baseline after termination of the same infusion.

$= (C_0 - C_t) \cdot 100/C_0$, where C_t is concentration at time t and C_0 is concentration at end of infusion.

To describe pharmacodynamic drug offset, the percentage minute ventilation recovery was calculated in each subject. The minute ventilation measured before administration of any drug was the baseline minute ventilation, and return to this minute ventilation measurement was considered to be 100% recovery. Thus percent recovery of minute ventilation was calculated as $\%MV \text{ recover} = (MV_t - MV_p) \cdot 100 / (MV_b - MV_p)$, where MV_t is minute ventilation at time t , MV_p is minute ventilation before end of infusion, and MV_b is minute ventilation baseline (before drug).

The percent decline in blood concentration or recovery of minute ventilation at each time for each patient was plotted against the time after drug infusion.

Percentage recovery in minute ventilation was analyzed by fitting the equation $y = a + b(1 - e^{-ct})$ to each patient's data, where y is percentage minute ventilation recovery, t is time in minutes after the drug infusion, e is the base of the natural logarithm, and a , b , and c are parameters estimated from the data. Time to 50% minute ventilation recovery, t_{50} , was calculated from this equation.

Percentage change in whole blood concentration was analyzed by fitting the equation $y = ae^{-bt}$ to each patient's postinfusion data, where y is percentage whole blood concentration decrease, t is time in minutes after

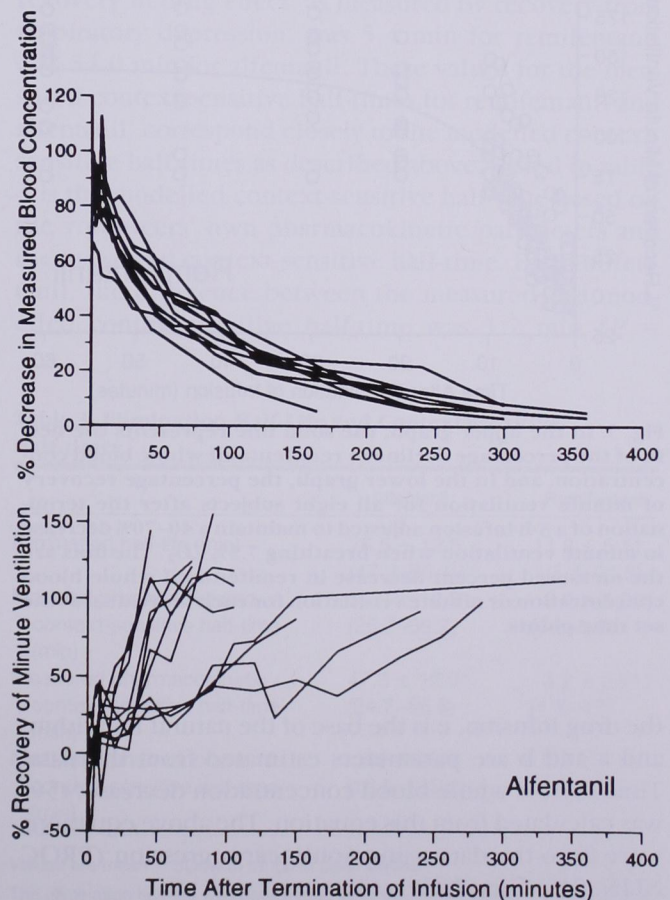


Fig. 4. The upper graph is the percentage decrease in alfentanil whole blood concentration of each subject after a 3-h infusion adjusted to maintain a 40–70% decrease in minute ventilation when breathing 7.5% CO₂. The lower graph is the percentage recovery of minute ventilation toward the predrug baseline after termination of the same infusion.

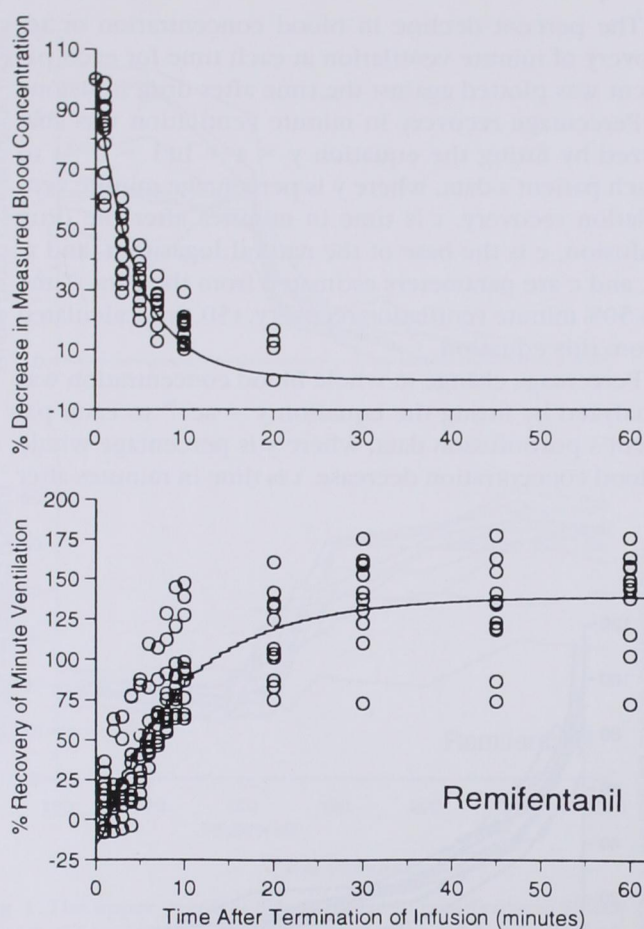


Fig. 5. In the upper graph, the solid line represents the best fit of the percentage decline in remifentanyl whole blood concentration, and in the lower graph, the percentage recovery of minute ventilation for all eight subjects after the termination of a 3-h infusion adjusted to maintain a 40–70% decrease in minute ventilation when breathing 7.5% CO₂. The dots are the measured percent decrease in remifentanyl whole blood concentration or minute ventilation for each individual at the set time points.

the drug infusion, e is the base of the natural logarithm, and a and b are parameters estimated from the data. Time to 50% whole blood concentration decrease, t_{50} , was calculated from this equation. The above equations were fit to the data using nonlinear regression (PROC NLIN, SAS, Cary, NC).

A two-stage pharmacokinetic analysis was performed on the concentration *versus* time data to fit a two- or three-compartment model. The geometric mean of the individual values was used to provide the mean population values for each parameter. These mean values

were then used to determine the elimination half-life. The individuals derived pharmacokinetic parameters were used to recalculate each volunteer's predicted context-sensitive half-time.

Other than for the pharmacokinetic parameters, summary statistics are listed as the mean and standard deviation for each parameter estimate. The elimination half-life was compared to the context-sensitive half-time using an unpaired Student's t test. The half-lives and half-times between the two drugs were similarly compared. A $P < 0.01$ was considered significant.

Results

Eight subjects, four from each drug group, were withdrawn from the study, because their minute ventilation values were not within the 40–70% depression from baseline within the prescribed 60 min, despite two adjustments in target concentrations. The remaining volunteers consisted of 22 (11 per group) ASA physical status 1 males, ranging in age from 19 to 35 yr (mean 25.4 ± 4.6) and weight from 66.4 to 93.4 kg (mean 77.5 ± 8.0). In 26 subjects, there was a sufficient number of measured blood concentrations to derive pharmacokinetic parameters.

The decrease in whole blood concentration and recovery in minute ventilation for remifentanyl after the termination of the infusion is presented in figure 1. Similarly, the decrease in whole blood concentration and recovery in minute ventilation for alfentanil after the termination of the infusion is presented in figure 2. The percentage decrease in whole blood concentration and percentage recovery of minute ventilation of each subject against time after termination of the remifentanyl infusion is shown in figure 3 and for alfentanil in figure 4. The fitted function of percent recovery in minute ventilation and decrease in measured blood concentration used to estimate the measured context-sensitive half-time for remifentanyl is presented in figure 5 and for alfentanil in figure 6. The measured time to 50% decrease in blood drug concentration after drug infusion, *i.e.*, the pharmacokinetic half-time, was 3.2 ± 0.9 min for remifentanyl and 47.3 ± 12.0 min for alfentanil ($P < 0.01$). The measured time to 50% recovery in minute ventilation after termination of drug infusion, the pharmacodynamic half-time, was 5.4 ± 1.8 min for remifentanyl and 54.0 ± 48.1 min for alfentanil ($P < 0.01$).

MEASURED CONTEXT-SENSITIVE HALF-TIME

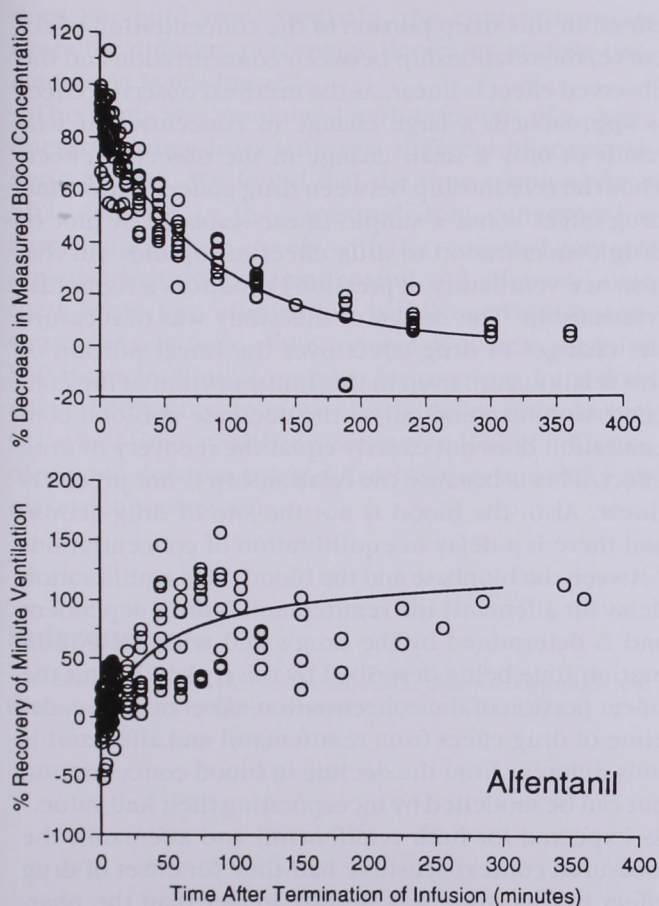


Fig. 6. In the upper graph, the solid line represents the best fit of the percentage decline in alfentanil whole blood concentration, and in the lower graph, the percentage recovery of minute ventilation for all eight subjects after the termination of a 3-h infusion adjusted to maintain a 40–70% decrease in minute ventilation when breathing 7.5% CO₂. The dots are the percent decrease in alfentanil whole blood concentration or minute ventilation for each individual at the set time points.

In table 3, the elimination half-lives and the context-sensitive half-times derived from the pharmacokinetic parameters of the volunteers participating in the study are compared to the context-sensitive half-times measured in these individual subjects after a 3-h infusion of either remifentanil or alfentanil. The measured context-sensitive half-time for both remifentanil and alfentanil was significantly different from their respective elimination half-life ($P < 0.01$). Both the elimination half-life and the context-sensitive half-times for remifentanil were significantly shorter than those for alfentanil.

Discussion

The elimination half-life of alfentanil from the pharmacokinetic parameters of Scott and Stanski is 111 min.⁶ Based on computer modelling, the context-sensitive half-time for alfentanil (using these pharmacokinetic parameters) after a 3-h infusion is predicted to be 59.4 min.² Similarly, using the pharmacokinetics described by Glass *et al.*, the elimination half-life of remifentanil was 9.5 min, and the predicted context-sensitive half-time was 2.45 min.³

We found that, after a 3-h infusion of remifentanil or alfentanil, designed to closely maintain a constant drug concentration and drug effect, the measured times to 50% decline in drug concentration as 3.2 min for remifentanil and 47.3 min for alfentanil, and for a 50% recovery in drug effect, as measured by recovery from respiratory depression, was 5.4 min for remifentanil and 54.0 min for alfentanil. These values for the measured context-sensitive half-times for remifentanil and alfentanil, correspond closely to the modelled context-sensitive half-times as described above. Listed in table 3 is the modelled context-sensitive half-time based on the volunteers' own pharmacokinetic parameters and the measured context-sensitive half-time. For remifentanil, the difference between the measured and modelled context-sensitive half-time was 1.2 min ($P =$

Table 3. Elimination Half-Life and Context-sensitive Half-times

	Alfentanil	Remifentanil
Elimination half-life (min)	76.5 ± 12.6 (47.3–96.1)	11.8 ± 5.1† (5.4–21.3)
Modeled pharmacokinetic context-sensitive half-time (min)	51.9 ± 12.3* (25.7–69.7)	2.0 ± 1.5*† (0.6–5.0)
Measured pharmacokinetic context-sensitive half-time (min)	47.3 ± 12.0* (24.7–66.6)	3.2 ± 0.9*† (1.8–4.7)
Measured pharmacodynamic context-sensitive half-time (min)	54 ± 48.1 (12.5–156.6)	5.4 ± 1.8† (1.8–7.5)

Values are mean ± SD (with range in parentheses).

The elimination half-life was determined from the volunteers participating in the study. The modeled pharmacokinetic context-sensitive half-time was determined from the volunteer's pharmacokinetic parameters. The measured pharmacokinetic context-sensitive half-time is the value obtained from the fitted curve of the actual measured concentrations obtained at the termination of the 3-h infusion.

* $P < 0.01$ versus elimination half-life of the same drug.

† $P < 0.01$, alfentanil versus remifentanil.

0.03). These two values are not the same, because the target concentrations were adjusted in some of the volunteers to obtain and maintain a steady effect; thus, the true measured half-time does not exactly represent the modelled context-sensitive half-time. In addition, blood samples for drug concentration were taken at 1-min intervals. This relatively slow sampling rate for remifentanyl may have limited our ability to define precisely its measured context sensitive half-time and thereby contributed to the observed difference between the measured and the modelled context-sensitive half-time.

This is the first attempt to measure the context-sensitive half-times for infusion drugs, since this concept was proposed as a more practical description of post-infusion pharmacokinetics. The principle underlying the context-sensitive half-time is that, for drugs exhibiting multicompartment pharmacokinetics, the net distribution of drug into or out of the peripheral compartments varies according to the duration of infusion. After drug infusions of brief duration, the plasma drug concentration decreases rapidly because the central clearance processes are supplemented by continued net distribution of drug out of the plasma into the peripheral compartments. As the infusion duration increases, the peripheral compartment's drug concentrations near equilibration with the plasma drug concentration. Thus, the potential for reducing the plasma drug concentration by distribution mechanisms after the termination of the infusion is greatly reduced, thereby slowing the rate of plasma drug decrease. Importantly, even when the infusion is continued long enough for the drug concentrations in each of the compartments to be in equilibration, postinfusion kinetics are not well described by the "elimination half-life." This is demonstrated with remifentanyl, which was infused for far longer than the time necessary to achieve a steady-state, yet its measured context-sensitive half-time at 3 h was considerably shorter than its terminal elimination half-life, but close to its predicted context-sensitive half-time.

For the clinical use of these measures, the required degree of decrease in effect needs to be known. It is important to realize that the decrease in effect does not necessarily mirror the decrease in drug concentration. Initially, as the concentration of drug increases, there is minimal change in the observed effect. As drug concentration continues to rise, this changes, so that small increases in concentration result in large changes in

effect. In this steep portion of the concentration-effect curve, the relationship between concentration and the observed effect is linear. As the maximal observed effect is approached, a large change in concentration will result in only a small change in the observed effect. Thus the relationship between drug concentration and drug effect is not a simple linear response. A plot of drug concentration to drug effect for opioids (in this instance ventilatory depression) produces a sigmoidal relationship. The design of this study was to measure the changes in drug effect over the linear portion of this relationship. Even in this linear portion of the concentration response curve, the decrease in blood concentration does not exactly equal the recovery in drug effect. This is because the relationship is not precisely linear. Also, the blood is not the site of drug action, and there is a delay in equilibration of concentrations between the biophase and the blood. This equilibration delay for alfentanil and remifentanyl is drug-dependent and is determined by the drug's ke_0 with the equilibration time being described by the $t_{1/2}ke_0$.⁹ Over the linear portion of the concentration-effect response, decline of drug effect from remifentanyl and alfentanil is thus different from the decline in blood concentration but can be modelled by incorporating their ke_0 value.¹ As expected for both remifentanyl and alfentanil, the measured context-sensitive half-time for offset of drug effect in this study was slightly longer than the pharmacokinetic context-sensitive half-time. The measured value of the pharmacodynamic offset closely corresponded to the modelled context-sensitive half-time of the effect compartment. For drugs with a smaller ke_0 (or longer $t_{1/2}ke_0$), the difference between the pharmacokinetic and the pharmacodynamic context-sensitive half-time would be larger than that seen with remifentanyl or alfentanil. However, it must be emphasized that, if a patient has been overdosed with an opioid, the time taken for the drug concentration to decrease by 50% will not reflect the time for recovery of normal ventilatory drive. Minimal recovery will occur until the concentration of the opioid falls to within the steep portion of the concentration-response curve. The context-sensitive half-time is thus not always a predictor of recovery time. If dosing has been excessive, a far greater percentage of decline in drug concentration than 50% is required before adequate recovery will occur. Also, if dosing has been such that the plasma drug concentration has been continuously altered, the context-sensitive half-time by definition

MEASURED CONTEXT-SENSITIVE HALF-TIME

does not hold true. Similarly, the context-sensitive times for differing percentage decreases in drug concentration is not linear.¹

This study was conducted with infusions of a single duration, using drugs with very different pharmacokinetic profiles. We found that the time required for a 50% decrease in the measured drug concentration agreed much more closely with the modelled context-sensitive half-time of remifentanyl and alfentanil than their respective elimination half-lives. This demonstrates the relevance of the concept of context-sensitive half-times in clinical practice for recovery from drug effect. Ultimately, to more clearly define context-sensitive half-time, it will be necessary to look at infusions of varying duration using different drugs and different plasma concentrations.

References

1. Shafer SL, Varvel JR: Pharmacokinetics, pharmacodynamics, and rational opioid selection. *ANESTHESIOLOGY* 74:53-63, 1991
2. Hughes MA, Glass PSA, Jacobs JR: Context-sensitive half-time in multicompartment pharmacokinetic models for intravenous anesthetic drugs. *ANESTHESIOLOGY* 76:334-341, 1992
3. Glass PSA, Hardman D, Kamiyama Y, Quill TJ, Marton G, Donn KM, Grosse CM, Hermann D: Preliminary pharmacokinetics and pharmacodynamics of an ultra-short-acting opioid: Remifentanyl (G187084B). *Anesth Analg* 77:1031-1040, 1993
4. Egan TO, Lemmens HJM, Fiset P, Hermann DJ, Muir KT, Stanski DR, Shafer SL: The pharmacokinetics of the new short-acting opioid remifentanyl (G187084B) in healthy adult male volunteers. *ANESTHESIOLOGY* 79:881-892, 1993
5. Westmoreland CL, Hoke JF, Sebel PS, Hug CC, Muir KT: Pharmacokinetics of remifentanyl (G187084B) and its major metabolite (G190291) in patients undergoing elective inpatient surgery. *ANESTHESIOLOGY* 79:893-903, 1993
6. Scott JC, Stanski DR: Decreased fentanyl and alfentanil dose requirements with age: A simultaneous pharmacokinetic and pharmacodynamic evaluation. *J Pharmacol Exp Ther* 240:159-161, 1987
7. Glass PSA, Jacobs JR, Smith IL, Ginsberg B, Quill TJ, Bai SA, Reves JG: Pharmacokinetic model-driven infusion of fentanyl: Assessment of accuracy. *ANESTHESIOLOGY* 73:1082-1090, 1990
8. Afifi MS, Glass PSA, Cohen NA, Shook JE, Camporesi EM: Depression of ventilatory responses to hypoxia and hypercapnia after pentamorphine. *Anesth Analg* 71:377-383, 1990
9. Sheiner LB, Stanski DR, Vozeh S, Miller RD, Ham J: Simultaneous modelling of pharmacokinetics and pharmacodynamics: Application to d-tubocurarine. *Clin Pharmacol Ther* 25:358-371, 1979