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The Pharmacodynamic Effect of a Remifentanil Bolus on Ventilatory Control

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Background: **In doses typically administered during conscious sedation, remifentanil may be associated with ventilatory depression. However, the time course of ventilatory depression after an initial dose of remifentanil has not been determined previously.**

Methods: **In eight healthy volunteers, the authors determined the time course of the ventilatory response to carbon dioxide using the dual isohypercapnic technique. Subjects breathed *via* mask from a to-and-fro circuit with variable carbon dioxide absorption, allowing the authors to maintain end-tidal pressure of carbon dioxide ($P_{ET_{CO_2}}$) at approximately 46 or 56 mmHg (alternate subjects). After 6 min of equilibration, subjects received 0.5 μg/kg remifentanil over 5 s, and minute ventilation ($\dot{V}_E$) was recorded during the next 20 min. Two hours later, the study was repeated using the other carbon dioxide tension (56 or 46 mmHg). The $\dot{V}_E$ data were used to construct two-point carbon dioxide response curves at 30-s intervals after remifentanil administration. Using published pharmacokinetic values for remifentanil and the method of collapsing hysteresis loops, the authors estimated the effect-site equilibration rate constant (k_{eo}), the effect-site concentration producing 50% respiratory depression (EC_{50}), and the shape parameter of the concentration–response curve (γ).**

Results: **The slope of the carbon dioxide response decreased from 0.99 [95% confidence limits 0.72 to 1.26] to a nadir of 0.27 $l \cdot min^{-1} \cdot mmHg^{-1}$ [−0.12 to 0.66] 2 min after remifentanil ($P < 0.001$); within 5 min, it recovered to approximately 0.6 $l \cdot min^{-1} \cdot mmHg^{-1}$, and within 15 min of injection, slope returned to baseline. The computed ventilation at P_{ET} = 50 mmHg ($\dot{V}_E50$) decreased from 12.9 [9.8 to 15.9] to 6.1 l/min [4.8 to 7.4] 2.5 min after remifentanil injection ($P < 0.001$). This was caused primarily by a decrease in tidal volume rather than in respiratory rate. Estimated pharmacodynamic parameters based on computed mean values of $\dot{V}_E50$ included k_{eo} = 0.24 min^{-1} ($T_{1/2}$ = 2.9 min), EC_{50} = 1.12 ng/ml, and γ = 1.74.**

Conclusions: **After administration of 0.5 μg/kg remifentanil, there was a decrease in slope and downward shift of the carbon dioxide ventilatory response curve. This reached its nadir approximately 2.5 min after injection, consistent with the computed onset half-time of 2.9 min. The onset of respiratory depression appears to be somewhat slower than previously reported for the onset of remifentanil-induced electroencephalographic slowing. Recovery of ventilatory drive after a small dose essentially was complete within 15 min. (Key words: Carbon dioxide; conscious sedation; effect site.)**

REMIFENTANIL is a rapidly metabolized intravenous opioid that is well-suited for situations necessitating rapid changes in anesthetic depth or when the postoperative requirement for analgesia is of limited duration. The pharmacokinetic properties of remifentanil, based on the exponential decay in plasma concentration after a continuous infusion, are well-established.[1–3] Context-sensitive half-times, based on these parameters, indicate that remifentanil concentrations decrease rapidly, regardless of the rate or duration of remifentanil infusion.[4] The decrease in analgesia and ventilatory depression after discontinuation of remifentanil parallel the decrease in plasma concentration.[4] However, when an initial intravenous bolus dose of remifentanil is administered, the onset of analgesia and ventilatory depression is not instantaneous because it takes time for remifentanil to cross the blood–brain barrier and reach the "effect sites" within the central nervous system. We designed this study to characterize the time course of ventilatory depression after a typical loading dose of remifentanil.

Materials and Methods

Eight nonsmoking healthy volunteers (two women and six men), ranging in age from 23 to 31 yr and in weight from 61 to 102 kg, consented to participate in this Internal Review Board–approved study. Subjects abstained from alcohol and caffeine for 24 h and took nothing by mouth for at least 8 h before the start of the

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study. To minimize the effect of auditory stimulation during ventilatory testing, the supine subjects listened to quiet classical music *via* headphones. We monitored blood pressure *via* forearm cuff, electrocardiography (ECG), and oxygen saturation as measured by pulse oximetry (Sp_{O_2}; Ohmeda Boulder, CO; 3700, fast mode). A Datex (Helsinki, Finland) Capnomac I calibrated with three reference mixtures of carbon dioxide in oxygen continuously monitored end-tidal partial pressure of carbon dioxide ($P_{ET}CO_2$) and fractional inspired oxygen tension ($F_{I_{O_2}}$). Subjects breathed *via* mask from a to-and-fro circuit with variable carbon dioxide absorption, enabling us to keep $P_{ET}CO_2$ constant to within ± 1 mmHg, as previously described.[5] A Hans-Rudolph (Kansas City, MO) 3700 heated pneumotachograph with a Validyne (Northridge, CA) DP45 differential pressure transducer and electronic integrator determined ventilatory volumes at body temperature pressure, saturated (BTPS). Before each set of measurements we performed a three-point volume calibration and linearity check using a Collins (Braintree, MA) 3200 3-l super syringe. An analog-to-digital converter and a computer recorded breath-by-breath measurements of minute ventilation ($\dot{V}_E$), tidal volume (V_T), respiratory rate, Sp_{O_2}, and $P_{ET}CO_2$.

To determine the steady state ventilatory response to carbon dioxide, subjects breathed hyperoxic mixtures ($F_{I_{O_2}} > 0.6$) of oxygen in nitrogen with $P_{ET}CO_2$ held constant at approximately 46 or 56 mmHg for alternate subjects; these carbon dioxide tensions were chosen because they typically lie on the linear portion of the carbon dioxide ventilatory response curve. After keeping $P_{ET}CO_2$ constant for a 6-min equilibration period, we recorded baseline ventilation and $P_{ET}CO_2$ for an additional 2-min. While data collection continued, we administered 0.5 μg/kg intravenous remifentanil over 5 s. We continued to record breath-by-breath changes in ventilation for the next 20 min while adjusting the flow of gas through the carbon dioxide absorber to maintain $P_{ET}CO_2$ as close as possible to the desired value (typically within ± 1 or 2 mmHg). Small volumes (≈ 300 ml/min) of oxygen were added to the circuit as needed to maintain a constant circuit volume. After a 2-h recovery period, we repeated the steady state and hypoxic ventilatory measurements at the alternate $P_{ET}CO_2$ (56 or 46 mmHg), whichever was not used previously.

Data Analysis

Because of the inherent variability of breath-by-breath ventilatory measurements, we used five-breath average values of $\dot{V}_E$, V_T, and $P_{ET}CO_2$ throughout the data analysis.

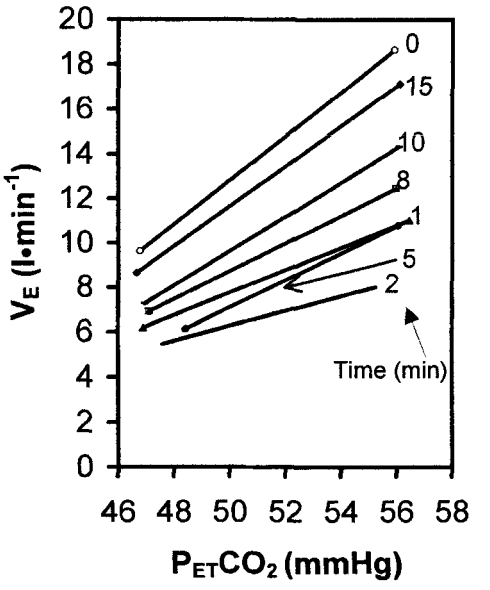

Fig. 1. Constructed carbon dioxide response curves before (time = 0) and at selected times after injection of 0.5 μg/kg remifentanil. These curves are based on mean values for $\dot{V}_E$ and $P_{ET}CO_2$ at each time point.

Starting at the time of injection (T = 0), we evaluated ventilation data at 30-s intervals for 20 min. For each subject, we determined two-point carbon dioxide ventilatory response curves ($\dot{V}_E$ *vs.* $P_{ET}CO_2$) at each 30-s interval after remifentanil injection: A line was drawn between the point representing $\dot{V}_E$ and $P_{ET}CO_2$ at a given time during the first "run" and the point describing these variables at the corresponding time during the second "run" (fig. 1).[6] To summarize the data, we described each of these lines in terms of its slope and the $\dot{V}_E$ at $P_{ET}CO_2$ = 50 mmHg ($\dot{V}_E50$) at each time after remifentanil injection. (These values represent the "gain" and "set-point," respectively, of the ventilatory control system.) Similar computations using V_T *versus* $P_{ET}CO_2$ enabled us to compute the V_T at $P_{ET}CO_2$ = 50 mmHg (V_T50) at each time after injection. Repeated-measures analysis of variance (subjects × times) followed by protected least significant difference tests determined the times at which ventilatory variables were significantly lower than the baseline, with $P < 0.05$ indicating statistical significance.

To model the pharmacodynamics of remifentanil-induced ventilatory depression, we used published pharmacokinetic data for remifentanil to estimate the subjects' remifentanil blood concentration as a function of time after injection.[3] We assumed first-order transfer kinetics between the central compartment and the effec

site, and a sigmoidal relation between effect-site concentration C_e and the observed effect on $\dot{V}_E50$,

$$\dot{V}_E50 = \dot{V}_E50_0 + (\dot{V}_E50_{MIN} - \dot{V}_E50_0)\frac{C_e^\gamma}{EC_{50}^\gamma + Ce^\gamma}$$

where $\dot{V}_E50_0$ is the baseline ventilation, V_E50_{MIN} is the $\dot{V}_E$ corresponding to maximum remifentanil-induced ventilatory depression (constrained to be ≥ 0), EC_{50} is the plasma concentration causing 50% depression of $\dot{V}_E50$, and γ is a dimensionless shape factor which determines the "steepness" of the dose-response curve. By using nonlinear least-squares estimation,[7]§ we minimized the least-squares difference between the ventilatory effect predicted based on the pharmacokinetic-pharmacodynamic model and observed effect (method of collapsing hysteresis loops).[3] This analysis yielded values for the onset rate constant k_{eo}, EC_{50}, and γ.

We performed the analysis in two ways:[1] On a subject-by-subject basis, we estimated the pharmacodynamic parameters; from these individual estimates we computed overall mean values with confidence limits.[2] We computed a single value for the pharmacodynamic parameters based on the mean values of the $\dot{V}_E50$ for all subjects *versus* the time data. We used the Pearson product moment correlation for individual and pooled data to determine the degree to which our model predicted the variations in the observed ventilatory data.

In addition, we computed the offset half-time (T_2) for remifentanil-induced depression of $\dot{V}_E50$ using nonlinear regression to estimate a standard, biexponential model:

$$\dot{V}_E = A_0 + A_1 \cdot e^{-0.693\frac{t}{T_1}} + A_2 \cdot e^{-0.693\frac{t}{T_2}}$$

All data are shown as the mean [95% confidence intervals], with $P < 0.05$ indicating statistical significance.

Results

After remifentanil administration, all subjects were mildly sedated, responsive to verbal command in normal tone, and had mild ptosis or a "glazed" appearance of the eyes. This corresponds to a change from 5 to 4 on the Observers Assessment of Alertness/Sedation Scale (OAA/S).[8] None of the subjects lost consciousness or became apneic during the study, and no subject had an Observers Assessment of Alertness/Sedation Scale score lower than 4 at any time.

§ PKPD Tools with XLMEM are available free of charge from Charles Minto and Thomas Schnider.[7]

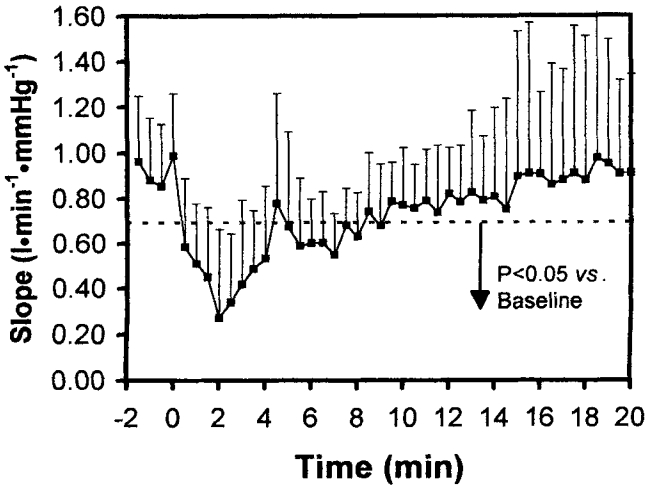

Fig. 2. Time course of the slope of the ventilatory response to carbon dioxide after injection of remifentanil 0.5 μg/kg. Values below the dotted line differ significantly ($P < 0.05$) from baseline. Error bars indicate the upper 95% confidence limit.

After the injection of remifentanil, V_E decreased at low (≈ 46 mmHg) and high (≈ 56 mmHg) carbon dioxide tensions (fig. 1). The decrease in the slope of the carbon dioxide response achieved significance within 30 s, decreasing from 0.99 [0.72 to 1.26] to 0.58 $l \cdot min^{-1} \cdot mmHg^{-1}$ [0.28 to 0.89] ($P < 0.05$) before reaching its nadir of 0.27 $l \cdot min^{-1} \cdot mmHg^{-1}$ [−0.12 to 0.66] ($P < 0.001$) 2 min after injection (fig. 2). The transient increase in slope between 4 and 5 min resulted from a slightly greater increase at the high carbon dioxide level, as compared with the corresponding increase at low carbon dioxide; however the position of the carbon dioxide response remained below baseline. Slope remained significantly depressed for approximately 9 min after remifentanil injection, but, within 15 min, it returned to baseline.

Similarly, $\dot{V}_E50$ decreased significantly within 30 s of injection from a baseline of 12.9 [9.8 to 15.9] to 10.5 l/min [7.8 to 13.2], reaching a nadir of 6.1 l/min [4.8 to 7.4] 2.5 min after injection. As shown in figure 3, $\dot{V}_E50$ remained significantly lower than baseline for approximately 12 min after remifentanil injection; within 15 min, $\dot{V}_E50$ returned to the preremifentanil baseline. The decrease in $\dot{V}_E50$ resulted primarily from a decrease in V_T (V_T50), as shown in figure 4. There was a small, transient decrease in respiratory rate: From its initial value of 14.1 breaths/min [11.3 to 16.9], it reached a nadir of 11.9 breaths/min [9.8 to 13.9] 1 min after remifentanil ($P <$

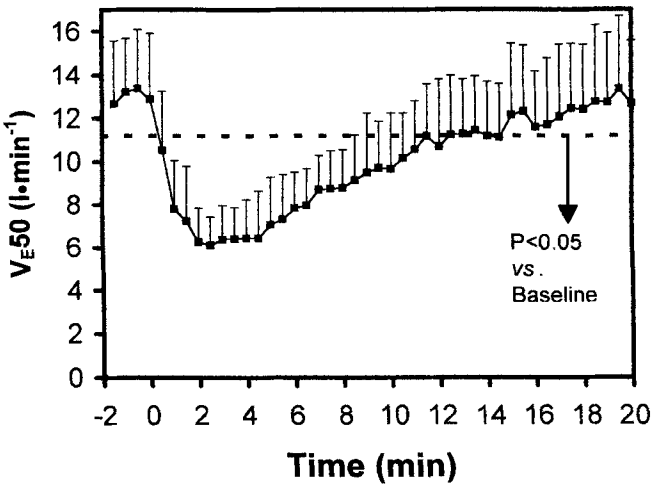

Fig. 3. Time course of the computed ventilation at $P_{ET_{CO_2}}$ = 50.0 mmHg. Values below the dotted line differ significantly (P < 0.05) from baseline. Error bars indicate the upper 95% confidence limit.

0.05 *vs.* baseline); by 2.5 min after injection, respiratory rate exceeded 13 breaths/min and no longer differed significantly from baseline.

Comparison of figures 2 and 3 revealed that the mean values of $\dot{V}_E50$ resulted in a much smoother curve than those of the carbon dioxide response slope. Therefore, we performed the pharmacodynamic analysis using $\dot{V}_E50$ to model the effect-site response. Table 1 shows the mean of the subjects' pharmacodynamic parameters (with confidence limits) and the pharmacodynamic parameters derived from the mean $\dot{V}_E50$ curve shown in figure 3. Figure 5A shows how the mean values of $\dot{V}_E$ compared with the plasma concentrations and pharmacodynamic effects predicted by the model, whereas figure 5B shows the relation between computed effect-site concentration and the measured values of $\dot{V}_E50$ as well as those predicted by the sigmoidal model.

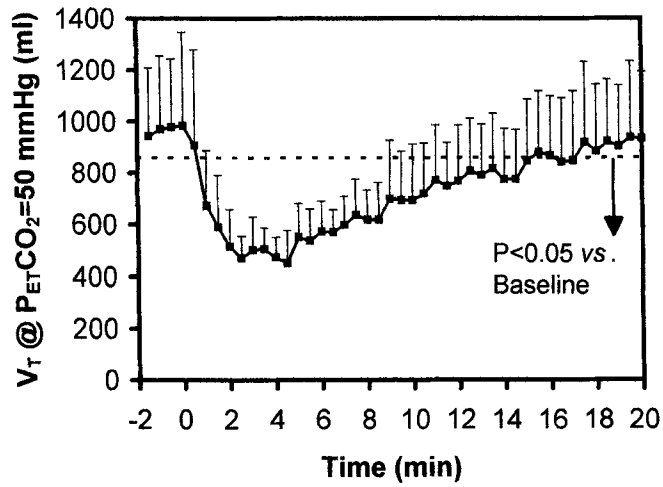

Fig. 4. Time course of the computed tidal volume at $P_{ET_{CO_2}}$ = 50.0 mmHg. Values below the dotted line differ significantly (P < 0.05) from baseline. Error bars indicate the upper 95% confidence limit.

Table 1. Derived Pharmacodynamic Parameters for the Effect of a Single Dose of Remifentanil, 0.5 μg/kg Intravenous, on $\dot{V}_E50$.

Parameter	Mean of Individual Values	Values Based on Pooled Data
k_{eo} (min^{-1})	0.34 [0.16, 0.52]	0.24
Equilibration		
$T_{1/2}$ (min)	2.04 [−0.24, 4.32]	2.88
EC_{50} (ng · ml^{-1})	1.36 [0.67, 2.05]	1.12
γ	2.45 [1.16, 3.75]	1.74
r^2	0.90 [0.60, 0.94]	0.99

Values are shown as the mean (95% confidence intervals), except for r^2, which is shown as median [range].

The time course of $\dot{V}_E50$ after remifentanil was closely approximated (r^2 = 0.99) by a biexponential function determined using nonlinear regression (fig. 6). On the basis of this regression, the $T_{1/2}$ for recovery from remifentanil-induced depression of $\dot{V}_E50$ was 6.2 min [4.3, 8.0].

Discussion

Remifentanil is an ultra-short-acting opioid that relies on plasma esterases for rapid metabolism. Its short duration of action makes it an ideal agent to administer by continuous infusion. To most rapidly achieve steady state plasma concentrations, continuous infusions generally are initiated with a loading dose. With remifentanil, the recommended loading dose for monitored anesthesia care (0.5–1.0 μg/kg) can create a situation in which patients are apneic yet awake; they must be encouraged to breathe for a few minutes until Pa_{CO_2} increases to the new apneic threshold.

To avoid this situation, the manufacturer (Glaxo Wellcome, Research Triangle Park, NC) recommends that the loading dose be administered over 30 s. Our data show that maximum ventilatory depression occurs approximately 2.5 min after a single loading dose is administered. This suggests that additional remifentanil administered within 2.5 min of the initial dose may produce further, unanticipated ventilatory depression, which is potentially dangerous in patients whose airways are not controlled. When the loading dose is followed by an

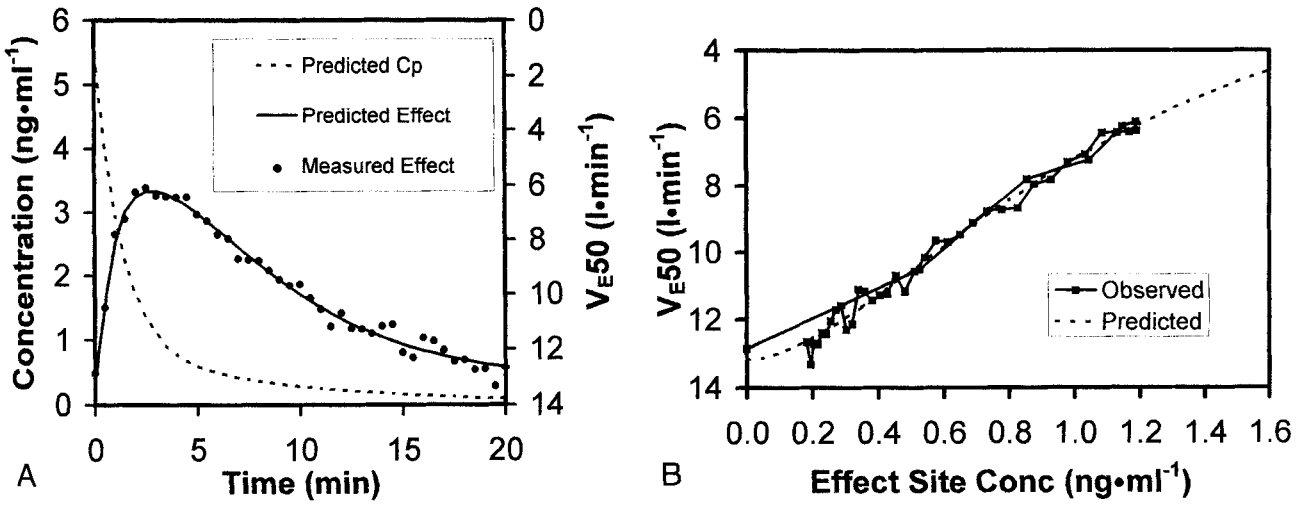

Fig. 5. (*A*) Time course of predicted plasma concentration (Cp), predicted pharmacodynamic effect, and the corresponding values of $\dot{V}_E50$ (measured effect) in the subjects. (*B*) Relation between effect-site concentration (from the pharmacokinetic–pharmacodynamic model) and the observed $\dot{V}_E50$ in the subjects. The dotted line is the sigmoidal function that predicts $\dot{V}_E50$ from the effect-site concentration.

infusion of remifentanil at 0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$, our pharmacodynamic model predicts that peak respiratory depression will occur approximately 5 min after the initial injection, and additional bolus doses of remifentanil during this time may be expected to exacerbate ventilatory depression.

By using spectral analysis of the EEG as a measure of the effect of remifentanil on the central nervous system, Egan *et al.* observed an onset $T_{1/2}$ of 1.6 min.[3] This is approximately 60% of the $T_{1/2}$ that we observed for respiratory depression. This difference may be related in part to the fact that the surface EEG and ventilatory drive depend on different neural pathways; it also may be related to the finding that, in the previous investigation, much larger doses of remifentanil (30–60 $\mu g/kg$) were administered. Differing blood flows, blood–brain barrier characteristics, and neural responsiveness to opioids may contribute to a difference in the time necessary for pharmacodynamic effects to develop. The fact that the EC_{50} for ventilatory depression, 1.1 ng/ml, was appreciably lower than the 19.9 ng/ml reported by Egan *et al.* for EEG spectral edge depression[3] suggests that there are significant regional differences in opioid responsiveness within the central nervous system. This also corresponds to the clinical observation that patients may be apneic yet awake after intravenous administration of rapidly acting opioids.

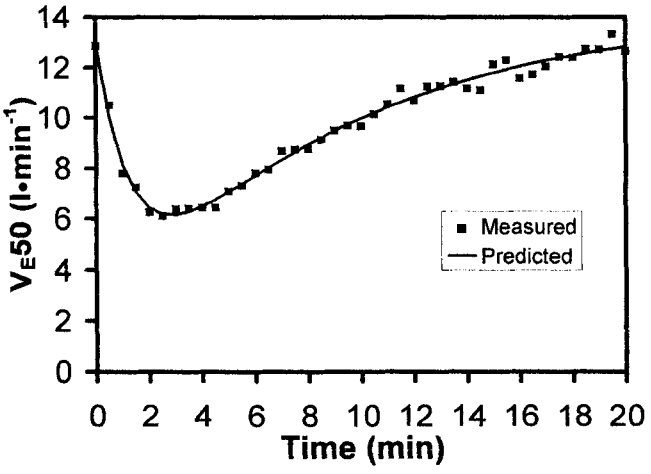

Fig. 6. Nonlinear biexponential regression of $\dot{V}_E50$ *versus* time, used to determine the offset $T_{1/2}$ for remifentanil. The measured values are shown to indicate the closeness of the exponential approximation.

Kapila *et al.* characterized the pharmacodynamic effect of remifentanil by monitoring recovery of $\dot{V}_E$ at $F_{ET}CO_2$ = 7.5% after a 3-h infusion.[4] In that context, they found the offset $T_{1/2}$ to be 5.4 min. This is similar to the offset $T_{1/2}$ of 6.2 min observed in the current study, confirming that the recovery from the ventilatory effect of remifentanil essentially is independent of the duration of administration. Dershwitz *et al.* also followed ventilatory drive by measuring $\dot{V}_E$ at $FiCO_2$ = 7.5% before, during, and after a 4-h remifentanil infusion.[9] Based on their pooled data, these investigators found that EC_{50} was 3.4 ng/ml in healthy subjects. Despite constant plasma concentrations, they observed a gradual decrease

in respiratory depression during remifentanil infusion, suggesting that some degree of tolerance was developing. Acute tolerance may explain why the EC_{50} for $\dot{V}_E$ that we observed after a single dose of remifentanil was appreciably lower than the EC_{50} observed after a 3- or 4-h infusion.

When remifentanil is used during general anesthesia with an established airway, ventilatory depression is not a major concern. However, when it is used as an analgesic in awake patients during monitored anesthesia care, the ventilatory depressant effects of remifentanil pose certain challenges. For example, ventilatory depression is not instantaneous; this mandates waiting a sufficient period of time ($\approx$ 2.5 min) for the peak effect of first dose to develop before additional remifentanil is administered to avoid the risk of "stacking" doses and producing apnea. The finding that our subjects did not become apneic despite rapid administration of remifentanil suggests that stimulation of ventilation with a modest concentration ($\approx$ 4%) of carbon dioxide might prevent apnea when remifentanil is administered for monitored anesthesia care.

The "dual isohypercapnic" method enabled us to determine ventilatory drive at 30-s intervals after remifentanil injection. Step-ramp rebreathing methods (*e.g.*, Read rebreathing technique)[10] take several minutes to accomplish and necessitate a resting period between determinations, making them unsuitable for assessing rapid changes in ventilatory drive after a single dose of a short-acting drug. By measuring ventilatory drive in the 46- to 56-mmHg range, we reduced the likelihood of being on the "hockey stick" portion of the carbon dioxide response curve; this was confirmed by the finding that none of the subjects became apneic at either carbon dioxide tension after remifentanil.

A potential shortcoming of our study is that we did not measure plasma remifentanil levels directly; rather, we relied on previously published pharmacokinetic parameters to predict plasma concentrations in the subjects. Although there is significant interindividual variability in these parameters, the effect of this variability can be minimized by using pooled rather than individual data to perform the pharmacodynamic modeling. In fact, pharmacokinetic variability may help to explain the great variability in pharmacodynamic values that we observed when these were calculated using individual rather than pooled data.

In summary, we found that, in doses typically used during monitored anesthesia care, a single dose of remifentanil causes both a downward shift and a decrease in the slope of the ventilatory response to carbon dioxide. The onset $T_{1/2}$ for ventilatory depression was of longer duration than that reported for EEG depression, and peak ventilatory depression occurred approximately 2.5 min after remifentanil injection, suggesting that it is necessary to wait at least this long to assess ventilatory effects before administering additional medication. Recovery of ventilation was essentially complete within 15 min, consistent with the short elimination half-life of remifentanil. Differences between the EEG and ventilatory effects of remifentanil, as reflected in onset time and EC_{50} help to explain the clinical observation that remifentanil may cause apnea in patients who are awake and responsive to verbal command.

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