Opioid therapy : a trade-off between opioid-analgesia and opioid-induced respiratory depression

Boom, M.C.A.

CHAPTER 3

MODELING THE NON-STEADY STATE RESPIRATORY EFFECTS OF REMIFENTANIL IN AWAKE AND PROPOFOL SEDATED HEALTHY VOLUNTEERS

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3.1 INTRODUCTION

Opioids affect breathing by activation of μ-opioid receptors expressed on respiratory neurons in the brainstem.[1,2] As a consequence ventilation is depressed and arterial carbon dioxide increases. Since carbon dioxide activates chemoreceptors in the neck and brainstem (peripheral and central chemoreceptors), part of the opioid-induced respiratory depression is concealed by carbon dioxide-induced respiratory stimulation (the so-called carbon dioxide chemoreflex).[3] Especially, when the opioid slowly passes into the brain, the subsequent slow increase in carbon dioxide will offset major respiratory depression. On the other hand, when the opioid rapidly passes the blood-brain barrier or the opioid is overdosed, depression of the respiratory neurons is faster and more noticeable than the respiratory stimulation from the carbon dioxide increase.[3] Then the opioid's effect is most dangerous. In general, opioids are considered safe with about 0.5% of patients receiving opioids for treatment of acute pain requiring immediate treatment for sometimes life-threatening respiratory depression.[1] However, in specific patient groups this number is certainly much greater (e.g., patients with sleep-related apnea, obesity, muscle weakness, pulmonary disease). Furthermore, even in patients considered not at risk opioid-induced mortality still occurs.[4,5]

The number of studies on the effect of potent opioid analgesics on breathing is still limited. Even sparser are studies that quantify intravenous opioid effect on breathing using meaningfully parameterized pharmacodynamic models. The latter models are important as they allow, apart from the reliable description of opioid effect, the comparison among opioids (e.g. on potency), the study of drug-drug interaction, and prediction of specific breathing-related idiosyncrasies, such as the occurrence and duration of apnea. Current available models may be divided into two groups: 1. Steady-state models, where the end-tidal carbon dioxide concentration (PCO_2) is kept constant (by breath-to-breath manipulation of the inspired carbon dioxide concentration) and just the drug's effect on ventilation is measured (these models are also called open-loop models as the feedback loop between ventilation and arterial PCO_2 is broken –the loop is now open);[6-10] and 2. Non-steady-state models, in which the effect of the drug on arterial (or end-tidal) carbon dioxide and ventilation are both measured (these models are also called closed-loop models as the feedback loop between ventilation and arterial carbon dioxide remains active).[11-13] In contrast to steady-state models, non-steady-state models need to take into account the depressant effect that the opioid has on respiratory neurons in the brain causing the reduction of breathing and consequently the increase in arterial PCO_2, but also and equally important, these models need to take into account the stimulatory effect of carbon dioxide on breathing. Only when both components are properly incorporated in the model reliable estimates of the drug's respiratory potency are obtained and a prediction of its respiratory behavior can be made.[3]

We previously performed steady-state experiments and applied steady-state models to describe opioid-induced respiratory effects and their interaction with anesthetics

(sevoflurane, propofol).[9,10] While it allowed for the accurate description of the synergistic opioid-anesthetic interaction on breathing, this was unable to predict 'real-life' non-steady-state conditions such as occur when drug concentrations rapidly change. In the current study we performed non-steady-state experiments by applying increases in remifentanil concentration of different rates of rise. Experiments were performed in healthy volunteers in the awake condition and at the background of a low-dose propofol infusion. Next, we developed a non-steady-state pharmacokinetic-pharmacodynamic model of opioid-induced respiratory depression.

The control of breathing is a complex system using both feedback and feed forward control tools to maintain cellular homeostasis.[14] Hence, it is important to make choices when considering the site of action of opioid effect within the control system. We constructed a relatively simple model with drug concentration and end-tidal PCO_2 as input and measured inspired ventilation as output. Basic characteristics of the model are (i) it assumes that drug and carbon dioxide have opposing effects on breathing;[3] (ii) it is based upon the linear and well described relationship between carbon dioxide and ventilation, $\dot{V} = G\,(PCO_2 - B)$, where $\dot{V}$ is inspired minute ventilation, G is the gain of the ventilatory control system and B the extrapolated end-tidal PCO_2 at which apnea occurs (apneic threshold);[14-16] (iii) the opioid effect is on B, while anesthetic effect is on G (Fig. 1).[10] In our study, the model's behavior is tested to assess whether it accurately predicts apnea at finite opioid drug concentrations and whether all important model parameters are estimable (using a sensitivity analysis).

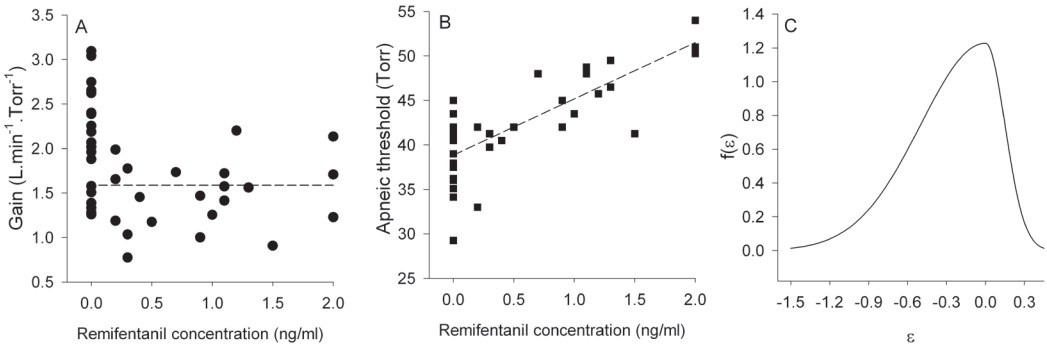

Figure 1. **A**. Effect of remifentanil on the central gain of the respiratory controller as measured by Nieuwenhuijs et al.[6] in steady-state experiments. At remifentanil concentrations > 0 the gain remains constant at 1.6 ± 0.1 $L.min^{-1}.Torr^{-1}$. **B**. Effect of remifentanil on the apneic threshold (B) of the respiratory controller as measured by Nieuwenhuijs et al.[5] B increases linearly with increasing remifentanil concentrations according to the function $B(C_{REM}) = 39*(1 + C_{REM}/6.14)$. **C.** Probability density function for end-tidal carbon dioxide concentration with $\sigma_A^2 = 0.0225$ and $\sigma_B^2 = 0.25$ (eqn. (9)).

3.2 MATERIALS AND METHODS

3.2.1 SUBJECTS

Ten healthy male volunteers (age 18-30 years; body mass index < 28 $kg.m^{-2}$) were recruited to participate in the study after approval of the protocol by the local Human Ethics Committee (Commissie Medische Ethiek, LUMC, Leiden, The Netherlands). Written and oral informed consent was obtained prior to inclusion in the study. All subjects were instructed not to eat or drink for at least 6 h before the study.

After arrival in the laboratory, an arterial line for blood sampling was placed in the left or right radial artery. In the contralateral arm an intravenous line was inserted for drug infusion. Each subject participated in three remifentanil infusions separated by 120 min washout-intervals. The first two were without a background infusion of propofol; the last with a propofol infusion aimed at a target bispectral index value of 80 (average target plasma concentration = 1 $\mu g.ml^{-1}$). We randomly assigned one of the two initial experimental runs (*i.e.*, without propofol infusion) to be performed without blood sampling. In the other two runs 3-6 arterial blood samples were obtained for remifentanil measurements at arbitrary time points.

Remifentanil was administered using a target controlled infusion system. For remifentanil we used a custom-built infusion pump that was programmed with a pharmacokinetic data set (Remifusor, University of Glasgow, Glasgow, UK).[17] We applied different remifentanil infusion schemes among the ten subjects as is described in table 1. We aimed at obtaining different rates of increases of the remifentanil plasma concentration (ranging from slow to fast). This was obtained by applying step increases in remifentanil plasma concentration (in 7 of 10 subjects we used steps of 1 $ng.ml^{-1}$) with varying step durations (0.5, 1, 1.5, 2, 3, 4 or 6 min) and with varying numbers of steps (2, 4, 5 or 6). In two subjects we performed a single 1-min step with step sizes of 6 and 9 $ng.ml^{-1}$. In the appropriate runs, one to three blood samples were randomly obtained during remifentanil infusion (but always just prior to a change in target remifentanil concentration); following infusion two to three blood samples were obtained, again at random times. Each volunteer was subjected to three identical target remifentanil infusion schemes. In case of irregular breathing with periods of apnea (no breathing for periods > 10 s) and/or significant oxygen desaturations (SpO2< 90%) the subject was initially stimulated to take a deep breath. If this had no effect the subject was artificially ventilated by bag via the mask and pneumotachograph for 20-30 s. The investigators could terminate or adapt the infusion at any time during the experiment when they felt that this was required to alleviate apnea and/or hypoxemia.

3.2.2 MEASUREMENTS

A face mask was applied over mouth and nose. Inspired and expired gas flows were measured with a pneumotachograph connected to a pressure transducer and electronically integrated to yield a volume signal (Hans Rudolph, Myandotta, MI).

During the studies the subjects inhaled 100% oxygen. The oxygen and carbon dioxide concentrations of the in- and expired gases and the arterial hemoglobin-oxygen saturation were measured with a Datex Multicap gas monitor (Datex-Engstrom, Helsinki, Finland). The electroencephalogram was recorded using an A-2000 monitor with software version 3.3 (Aspect Medical Systems, Norwood, MA). The monitor computed the bispectral index (BIS) over 2-s epochs. We averaged the BIS-values over 1-min. End-tidal PCO_2 and inspired minute ventilation were stored on disc for further analysis. We further report the measured SpO_2 and BIS during the remifentanil infusions.
Samples for the determination of blood remifentanil concentrations 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 assay method is based on tandem mass spectrometry detection.[10]

3.2.3 DATA ANALYSIS

A population pharmacokinetic-pharmacodynamic analysis was performed on the data. The analysis was performed in two steps. In step 1 a population remifentanil pharmacokinetic analysis was performed. Next using the individual Bayesian pharmacokinetic estimates a population pharmacodynamic analysis was performed.

Remifentanil pharmacokinetics. The description of remifentanil pharmacokinetics was aimed at obtaining individualized drug input functions to the pharmacological model. The actual infusion rates from the log file of the target controlled infusion device were used. The distributions of the structural parameters were fixed to the values of the three-compartmental model reported by Minto *et al.*[17] (*i.e.*, the typical values and interindividual variabilities), and individualized by adjusting for age and lean body mass. A population analysis was performed which allowed for Bayesian individualization of the structural parameters (albeit within the constrained distribution).[18] A remifentanil effect-site was postulated where the concentration lags with respect to the central compartment concentration as quantified by the equilibration half-life parameter $t_{½}k_{e0}$.

Carbon dioxide pharmacokinetics (figure 2). The relationship between carbon dioxide content (C) and its partial pressure (P) was assumed to be linear, so that $P = \lambda_0 \cdot C$, where $\lambda_0 = 0.863$ Torr.(ml CO_2 in 100 ml blood)$^{-1}$.[19] The following mass balance equations were used for the lungs and body (approximating the body by one compartment):

$$V_{AL} \cdot \frac{dP_A}{dt} = -\dot{V} \cdot P_A + \lambda_1 \cdot \dot{Q} \cdot (P_V - P_A)$$

$$V_{TS} \cdot \frac{dP_V}{dt} = \dot{Q} \cdot (P_A - P_V) + \lambda_2 \cdot \dot{V}_{CO_2}$$

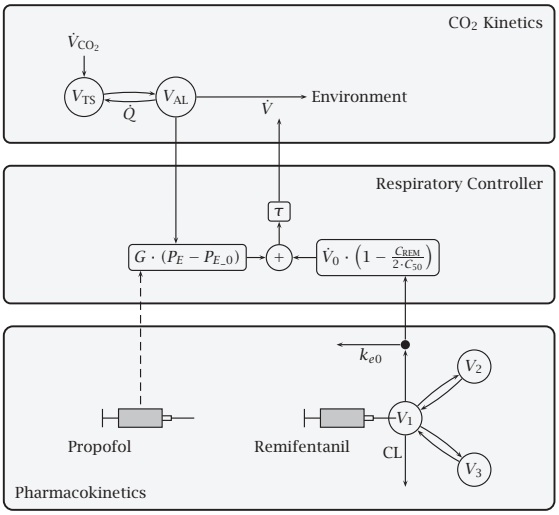

Figure 2. Schematic representation of the pharmacokinetic-pharmacodynamic model. The model has three distinct parts. I. The remifentanil pharmacokinetic part, consisting of the distribution of remifentanil though the body, including the effect-site (i.e., the respiratory controller in the brainstem) (via a rate constant, k_{e0}). Part II is the respiratory controller in the brainstem. Remifentanil's effect on the ventilatory control system results in a reduction of ventilation (via a delay, τ). Part III is the part that describes carbon dioxide kinetics. Carbon dioxide production determines together with ventilation the arterial carbon dioxide concentration. Since remifentanil causes the reduction of ventilation and carbon dioxide production is minimally affected, the ability of the system to clear carbon dioxide has diminished and arterial carbon dioxide concentrations will rise. This will have a stimulatory effect on the respiratory controller (part II). The main effect of adding propofol on top of remifentanil is shown as an effect on the gain factor G.

CL = clearance; C_{REM} = remifentanil concentration in plasma; C_{50} = concentration remifentanil causing 50% respiratory depression; G = gain of the ventilatory control system or slope of the hypercapnic ventilatory response; P_E = end-tidal carbon dioxide partial pressure; P_{E_0} = baseline (predrug) end-tidal carbon partial pressure; Q = cardiac output; k_{e0} = blood-effect site rate constant; τ = time constant of the ventilatory control system; $\dot{V}$= inspired minute ventilation; $\dot{V}_0$ = baseline (predrug) inspired minute ventilation; $\dot{V}_{CO2}$= carbon dioxide production; V_{ALV} = alveolar volume; V_{TS} = tissue volume; $V_{1\text{-}3}$ = volumes of compartments 1 to 3 of the kinetic remifentanil model.

where V_{AL} is alveolar volume, P_A arterial carbon dioxide pressure (which is assumed to equal alveolar pressure), $\dot{V}$ inspired minute ventilation, Q cardiac output, P_V venous carbon dioxide pressure, V_{TS} apparent tissue volume, and $\dot{V}_{CO2}$ is carbon dioxide production. Since ventilation enters the model of carbon dioxide kinetics directly (see eqn. 2) no correction was made for dead space ventilation. Furthermore, $\lambda_1 = k \cdot P_{BW}.\lambda_0^{-1} .100^{-1} \approx 10$ and $\lambda_2 = 100 \cdot \lambda_0$,, where k is the volume conversion factor from standard temperature and pressure, dry to body temperature and air saturated with water and P_{BW} the barometric pressure minus the pressure of air saturated with water. In the data analysis we fixed V_{AL} to 3L.[19] $V_{CO2}$was estimated from the baseline end-tidal carbon dioxide concentration and V. These baseline values, Q and V_{TS} were parameters to be estimated.

Pharmacodynamic analysis: Modeling the effect of remifentanil on the ventilatory control system (Fig. 2). The effect of end-tidal PCO_2 (P_E) on ventilation under hyperoxic conditions can be modeled as follows:[14-16]

$$\tau \frac{d\dot{V}}{dt} = G \cdot (P_E - B) - \dot{V} \qquad \text{eqn. (2)}$$

where G is the central gain, B the apneic threshold and τ a time constant. Nieuwenhuijs *et al*.[10] characterized the remifentanil-propofol interaction on the ventilatory control system using a response modeling approach. For the present study we re-analyzed those earlier data to characterize the effect of remifentanil on B and G (see Figs. 1A and B). From these analyses we estimated that at remifentanil concentration (C_{REM}) > 0, G remained constant while B increased linearly (the concentration remifentanil that doubles B is 6.14 ± 0.77 $ng.ml^{-1}$). Hence we assumed that in the current study remifentanil changed B but not G.

In the steady-state we have:

$$\dot{V}(C_{rem}) = G \cdot (P - B(C_{rem})) \qquad \text{eqn. (3)}$$

with

$$B(C_{rem}) = B_0 \cdot \left(1 + \frac{C_{rem}}{C_{100}}\right) \qquad \text{eqn. (4)}$$

where B_0 is the apneic threshold when $C_{REM} = 0$ and C_{100} the concentration remifentanil that causes a doubling of B. Rewriting equation 3 and defining baseline or resting end-tidal carbon dioxide concentration (*i.e.*, end-tidal PCO_2 before the remifentanil infusion) as P_{E_0} we get:

$$\dot{V}(C_{rem}) = G \cdot (P_{E\_0} - B(C_{rem})) + G \cdot (P_E - P_{E\_0}) \quad \text{eqn. (5)}$$

Baseline ventilation ($\dot{V}_0$) = $G \cdot (P_{E\_0} - B_0)$ and concentration remifentanil causing 50% respiratory depression, $C_{50,} = 0.5 \cdot C_{100} \cdot \frac{P_{E\_0} - B_0}{B_0}$. We then rewrite equation 6 into

$$\dot{V}(C_{\text{rem}}) = \dot{V}_0 \cdot \left(1 - \frac{C_{\text{rem}}}{2 \cdot C_{50}}\right) + G \cdot (P_E - P_{E\_0}) \qquad \text{eqn. (6)}$$

.

Note that C_{50} causes 50% depression of ventilation when $G.[P - P_{E\_0}] = 0$, which may occur when $P_E = P_{E\_0}$ (*e.g.*, after an acute remifentanil infusion when carbon dioxide did not rise as yet) or when G = 0 (as may occur when combining remifentanil with high propofol concentrations). This equation allows for the possibility of apnea at finite drug concentrations which is appealing from a clinical point of view. Finally, in eqn. (2) τ was fixed to 2.5 min.[15]

Modeling the end-tidal carbon dioxide pressure. End-tidal PCO_2 is (under 'normal' circumstances) an accurate indicator of alveolar PCO_2. However, close to apnea, the breathing pattern is such that end-tidal PCO_2 as measured by the gas monitor is likely to be inaccurate and possibly measured too low. So, if we write for the residual error:

$$P_E = \hat{P}_E + \epsilon \qquad \text{eqn. (7)}$$

where P_E is the measured value and $\hat{P}_E$ the predicted value. The variance of ε should be smaller (σ_A^2) when $P_E > \hat{P}_E$ and larger when (σ_B^2) when $P_E < \hat{P}_E$. Therefore the probability density of ε was written as:

$$f(\epsilon; \sigma_A, \sigma_B) = \begin{cases} \frac{2}{(\sigma_a + \sigma_B)\sqrt{2\pi}} \exp\left(\frac{-\epsilon^2}{2\sigma_A^2}\right) \\ \frac{2}{(\sigma_a + \sigma_B)\sqrt{2\pi}} \exp\left(\frac{-\epsilon^2}{2\sigma_B^2}\right) \end{cases} \qquad \text{eqn. (8)}$$

which is a continuously differentiable function and integrates to 1. Since the distribution of ε is asymmetric and the mean of $\varepsilon \neq 0$, $\hat{P}_E$ displayed in the figures is the mode. An example of the asymmetric probability density function with $\sigma_A^2 = 0.0225$ and $\sigma_B 2 = 0.25$ is given in figure 1C.

Furthermore, measured end-tidal carbon dioxide concentrations were determined to be missing values if they were lower than 37.5 Torr or when the corresponding measured ventilation was below 1 $L.min^{-1}$, because in those cases it can be expected that end-tidal PCO_2 is inaccurate.

Modeling minute ventilation. Minute ventilation (V) was assumed to be normally distributed with variance σ_v^2. However, during apnea manual ventilation (by mask) was applied. In that case the measured ventilation values were determined to be missing values but used for the uptake and distribution model of carbon dioxide.

Statistical Analysis. The models as described above were implemented in NONMEM VII (ICON Development Solutions, Ellicott City, MD).[18] The differential equations were solved with NONMEM's routine ADVAN6; the probability density functions (eqn. 8) were used with NONMEM'S LIKELIHOOD option. NONMEM VII's Markov Chain Monte Carlo Bayesian analysis method was used for parameter estimation. This method yields probability distributions of the model parameters from which means, standard errors and 95% confidence intervals can be obtained. Uninformative priors were used for the interindividual variability terms for the pharmacodynamic analysis (in the pharmacokinetic analysis these were fixed); no priors were required for the structural parameters because of the highly informative data. An interoccasion variability term was incorporated for both parameters, $\dot{V}_0$, and P_{E_0} (as their product is related to carbon dioxide production). Interindividual variability terms with a large standard error (larger than the estimate) were removed from the model. The burn-in samples were tested for convergence (all parameters and objective functions over 20 iterations, each 50 iterations apart; $P < 0.05$); 1000 iterations were used to obtain parameter distributions. Significance of factors representing a deviance of pharmacokinetic parameters from those obtained by Minto *et al.*,[17] and significance of factors representing a decrease in the pharmacodynamic model parameters G and C_{50} were tested by checking whether their 95% confidence intervals excluded 1.

3.2.4 SENSITIVITY ANALYSIS

A sensitivity analysis of a proposed model will indicate whether the parameter values of the model can be estimated with finite precision from the measured data.[20] Parameters may not be estimable for various reasons: because of the model structure, dependence on other parameters, or the specific input function chosen. We performed a sensitivity analysis of simulated data in which C_{REM} increases to 5 $ng.ml^{-1}$ in 5 steps using three distinct input functions: A. step size = 1 $ng.L^{-1}$, duration of step = 1 min; B. step size = 1 $ng.ml^{-1}$, duration of step = 5 min; C. step size = 1 $ng.ml^{-1}$, duration of step = 0.1 min. The analysis was performed by fixing one parameter *(i.e.* not allowing it to be estimated) at a time to a series of values (from 50% to 150%) of the 'best' value of the parameter. Next, the other parameters were estimated and the -2log likelihood (–2LL) values were determined. This so-called likelihood profile method will show whether any of the parameters are or are not estimable. If not, the curve of -2LL *versus* the fixed parameter values (the 'cost' function) will be flat.

3.2.5 SIMULATION STUDY

To get an indication of the effect of slowing the rate of rise of remifentanil on the nadir in ventilation or duration of apnea, we performed thirty simulations on remifentanil effect in the absence and presence of propofol. We simulated linear increases in remifentanil concentration at the effect site with rates of rise of 5 to 0.17 $ng.ml^{-1}.min^{-1}$. The infusion was terminated when the effect-site concentration had reached 5 $ng.ml^{-1}$.

3.3 RESULTS

All subjects completed the study without unintended effects. An example of one experimental run is given in Fig. 3; it is the data from one subject (id003) on the effect of a staircase increase in remifentanil concentration during a constant propofol infusion (run #3). The top panel shows the target increase in remifentanil plasma concentration to 4 $ng.ml^{-1}$. Note that the infusion was aborted early (due to the occurrence of apnea, panel C). Panel B shows the measured BIS values, panel C inspired minute ventilation per breath. BIS values were on average 80 indicating moderate sedation, in agreement with the observation that the subject was unresponsive to verbal command. Breathing reduced rapidly upon exposure to remifentanil and apnea occurred after 3 min. Apnea was followed by irregular and cyclic breathing which continued for 15 to 20 min, well after the remifentanil infusion was stopped. Note in panel D that during irregular breathing with low tidal volumes or apnea an accurate measurement of end-tidal carbon dioxide was not possible .

The infusion schemes applied in the studies are given in table 1. The estimated plasma concentration rates of rise varied from 0.17 to 9.0 $ng.ml^{-1}.min^{-1}$. BIS values were 93.2 ± 4.6 (mean ± SD) in remifentanil runs and 82.2 ± 4.8 ($P < 0.05$) in runs where remifentanil was given on top of propofol. The lowest values for SpO2 were 93.8 ± 7.2% in the remifentanil runs and 87.5 ± 8.4 % in the remifentanil-propofol runs ($P < 0.05$). Saturation values < 90% occurred on average 30 ± 41 s in the remifentanil runs and 110 ± 86 s in the remifentanil-propofol runs ($P = 0.05$). Apnea did not occur in remifentanil runs but in 8 remifentanil-propofol runs (averaged duration = 4.4 min, range 1 to 7 min). In runs of subjects 007 and 009 (remifentanil rates of rise 0.17 and 0.22 $ng.ml^{-1}.min^{-1}$) the duration of apnea was at its lowest range, 1 and 2 min respectively.

3.3.1 PHARMACOKINETIC ANALYSIS

To get an indication of the goodness of the pharmacokinetic data fits, we plotted the measured concentrations versus the individual and population predicted remifentanil concentrations (Fig. 4A and B). The plots indicate that the pharmacokinetic model adequately described the data. Two examples of pharmacokinetic data fits given in figure 4 are in agreement with this statement. The pharmacokinetic parameter estimates were not significantly different from those of Minto *et al.*[17] except for parameter V_2 (volume of compartment 2) which was a factor of 0.522 ± 0.125 (95% confidence interval 0.323-0.808)

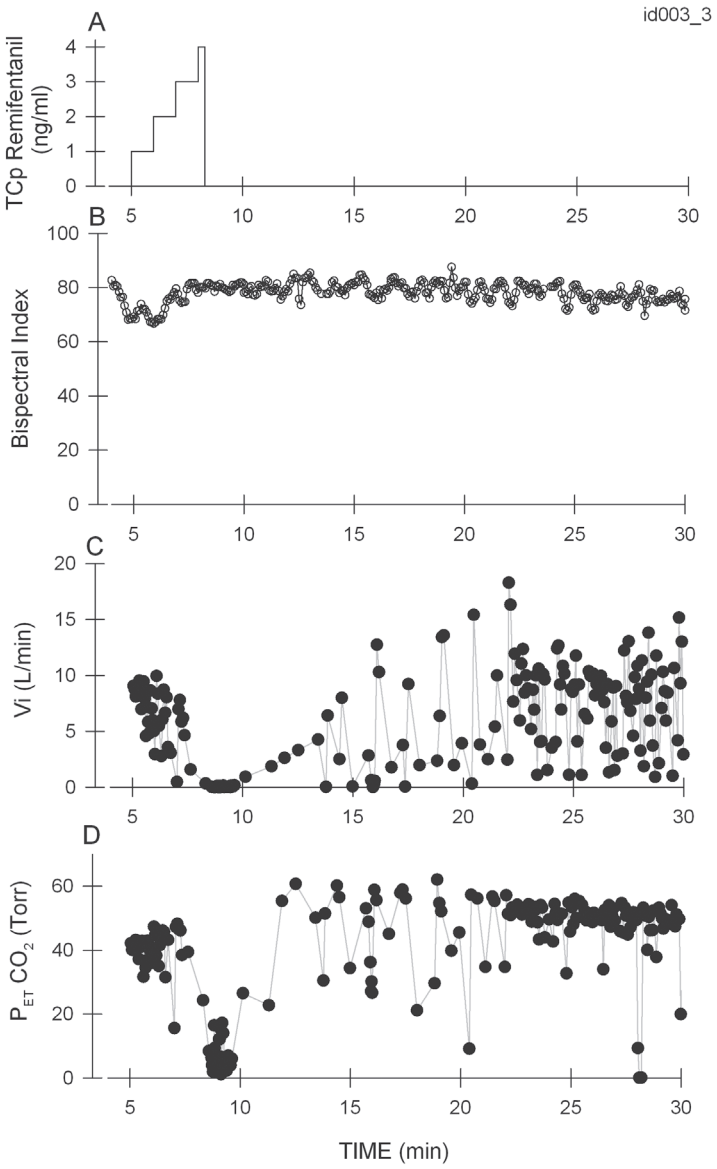

Figure 3. Example of the effect of remifentanil staircase infusion against the background of a constant propofol infusion. **A.** Target plasma remifentanil concentration (T_{CP}). **B.** Bispectral index (BIS). **C.** Measured inspired ventilation. Note that ventilation quickly reaches apneic values after the initiation of the remifentanil infusion. Next breathing remains irregular with a reduced breathing frequency and periods of cyclic breathing. To get an indication of the sequential breathing pattern the breaths are connected by a grey line. **D.** Measured end-tidal carbon dioxide concentration.

Table 1. Remifentanil infusion schemes

Subject #	Step size ($ng.ml^{-1}$)	Number of steps	Duration of step (min)	Total duration of infusion (min)	Max. target conc. ($ng.ml^{-1}$)	Remifentanil increase ($ng.ml^{-1}.min^{-1}$)
001	2.0	2	2	4	4.0	1.0
002	1.0	2	1.5	3	4.0	0.75
003	1.0	5	1	5	5.0	1.0
004	1.0	4	4	16	4.0	0.25
005	6.0	1	1	1	6.0	6.0
006	1.0	6	0.5	3.0	6.0	2.0
007	1.0	4	2	8	4.0	0.50
008	1.0	4	6	24	4.0	0.17
009	1.0	4	3	12	4.0	0.33
010	9.0	1	1	1	9.0	9.0

Table 2. Pharmacodynamic parameter estimates

	Estimate	SE	95% c.i.	ω2	SE	95% c.i.
$\dot{V}$ (L/min)	7.2	1.2	5.0-9.9	0.20	0.14	0.07-0.54
P_0 (Torr)	42.3	6.3	30.0-56.3	1.4	0.9	0.5-3.9
IOV				0.24	0.13	0.11-0.53
V_{TS} (L)	9.5	0.2	9.0-9.9	*	*	*
$t_{½}k_{e0}$ (min)	0.53	0.02	0.49-0.58	*	*	*
G ($L.min^{-1}.Torr^{-1}$)	0.42	0.01	0.40-0.44	*	*	*
C_{50} ($ng.ml^{-1}$)	1.6	0.03	1.5-1.67	0.14	0.10	0.05-0.34
Q ($L.min^{-1}$)	5.5	0.35	4.9-6.2	*	*	*
σ_A^2	0.044	0.0026	0.04-0.05			
σ_B^2	0.22	0.0069	0.21-0.23			
σ_v^2	5.55	0.11	5.4-5.8			
Propofol effect on G	0.46	0.015	0.43-0.49			
Propofol effect on C_{50}	0.84	0.030	0.79-0.90			

$\dot{V}_0$ is baseline ventilation (*i.e.*, ventilation prior to remifentanil infusion);

P_0 is baseline end-tidal PCO_2 (*i.e.*, end-tidal PCO_2 prior to remifentanil infusion);

IOV is the interoccasion variability (each subject participated in three distinct runs) based on the variability in $\dot{V}_{CO2}$, which was incorporated for V_0 and P_0;

V_{TS} is tissue volume (see eqn. 2);

$t_{½}k_{e0}$ is the blood-effect-site equilibration half-life for remifentanil; G is the central gain of the respiratory controller;

C_{50} is given the (effect-site) concentration remifentanil causing 50% depression of ventilation; Q is cardiac output;

σ_A^2 and σ_B^2 are variances of the residual error of PCO_2 (see eqn. (9)); σ_v^2 is the variance of ventilation;

Propofol effect: A significant effect (at the $P < 0.05$ level) of propofol was observed on G and C_{50}. The factor by which propofol was affected is the estimate given: Gc during the combined infusion of propofol and remifentanil was 0.46*[Gc observed during just remifentanil] = 0.46*0.42 = 0.19 $L.min^{-1}.Torr^{-1}$. Similarly for C_{50}, during the combinded remifentanil/propofol infusion C_{50} = 0.84*1.6 = 1.3 $ng.ml^{-1}$.

* not estimable.

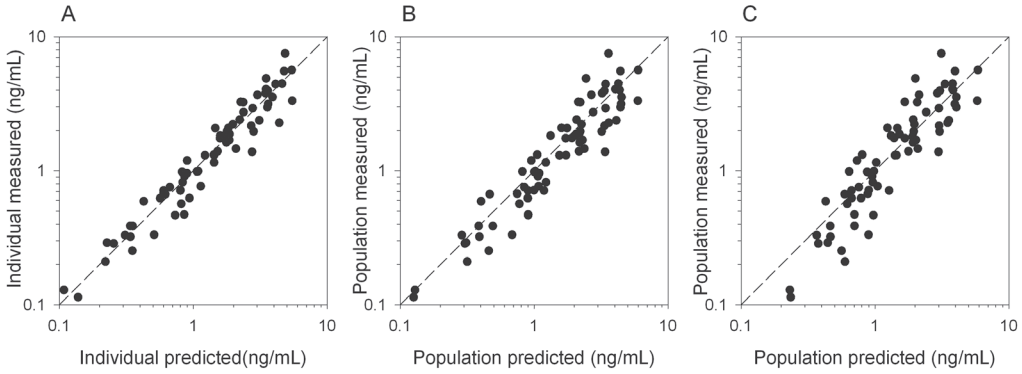

Figure 4. Goodness of fit plots for the pharmacokinetic model. **A** and **B** are the measured concentrations (y-axis) versus the individual (A) and population (B) predicted values. **C.** The pharmacokinetic analysis performed according to the parameter estimates of Minto *et al*.[17] (that is without a factor for V_2).

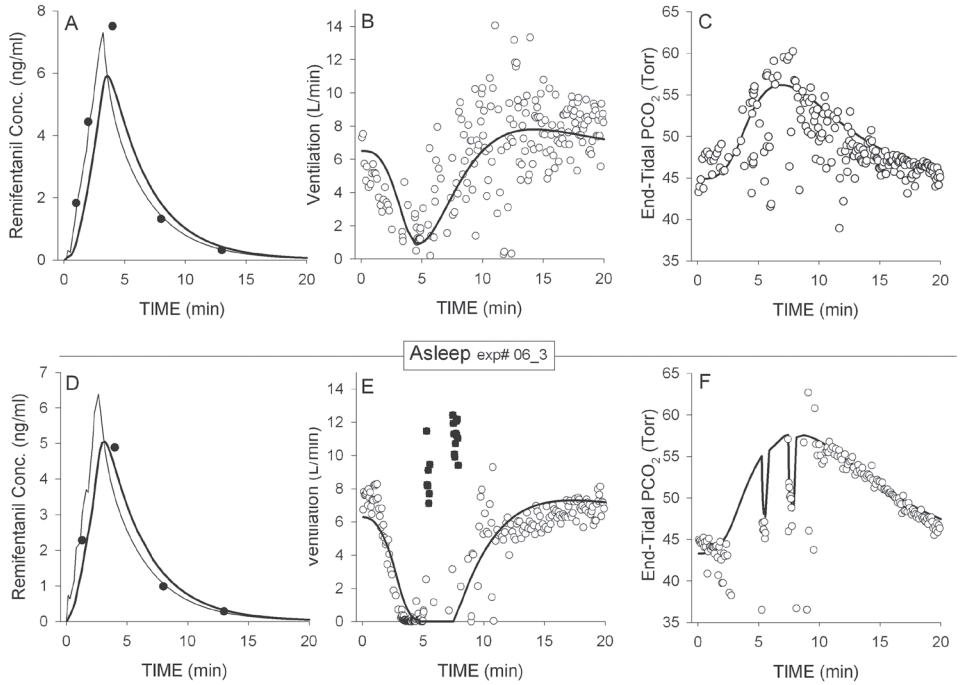

Figure 5. Examples of data fits of the effect of remifentanil on ventilation in one subject in the awake state (panels A-C) and asleep with propofol (panels D-F). **A** and **D**: Measured remifentanil concentration (closed circles), pharmacokinetic data fits (thin line), and estimated effect-site (thick line) concentrations. **B** and **E**: Minute ventilation with each spontaneous breath an open circle. Artificial breaths are depicted by closed squares. The lines through the data are the data fits. During sleep (panel E) the subject is apneic and requires artificial breathing assistance. **C** and **F**: End-tidal carbon dioxide values (open circles) and data fits. In panel F the effect of the artificial ventilation is clearly visible in the data fits.

of that of Minto *et al*. The factor in V_2 causes population measured versus population predicted concentrations to lie more closely on the line of identity. Without the factor, concentrations at the high end are underestimated and vice versa (figure 4C).

3.3.2 PHARMACODYNAMIC ANALYSIS

The pharmacodynamic model adequately described the data. Examples of data fits are given in Fig. 5. The data are from one subject (id006) and are fits of ventilation and end-tidal carbon dioxide concentrations under awake (panels A-C) and sedated (panels D-F) conditions. The effect of artificial ventilation by mask is clearly visible on end-tidal carbon dioxide in panel F as these periods of artificial ventilation were incorporated in the pharmacodynamic model. Since no spontaneous ventilation was observable during the period of artificial ventilation the fit through the ventilation data still (correctly) predicts apnea (Fig. 5E).

In table 2 the population pharmacodynamic model parameters are given. The concentration remifentanil causing 50% respiratory depression is 1.6 ± 0.03 ng.ml^{-1}. A notable observation is the low value for G in the remifentanil runs (0.42 L.min^{-1}.Torr^{-1}). Low-dose propofol significantly decreased parameters G by more than 50% to 0.19 L.min^{-1}.Torr^{-1}, and parameter C_{50} by about 20% to 1.3 ng.ml^{-1}. Propofol had no effect on baseline ventilation, baseline end-tidal carbon dioxide concentration, V_{TS}, Q and remifentanil $t_{½}k_{e0}$. All of these latter values were within the expected ranges.

3.3.3 SENSITIVITY ANALYSIS

The results of the likelihood profile method of the pharmacodynamic model are shown in figure 6. The Δ-2log likelihood (or the 'cost' function) indicates that the estimated model parameters (G, C_{50}, $t_{½}k_{e0}$, V_{TS}, Q) when applying relatively slow remifentanil input functions (that is, step durations of 1 and 5 min) were estimated with acceptable accuracy (± 10% of the actual value). Due to noise on the simulated data, deviations from optimal parameter values were sometimes observed (i.e., lower values of -2LL at 'optimal' parameter values that were different from those used in the simulation). Much faster infusion (step duration is 0.1 min) yielded a significant estimation bias. Since we applied mostly slow input functions (step duration 1 min or larger in 9 out of 10 subjects) we may assume that all important model parameters were estimable without any bias. Furthermore, visual inspection of the sensitivity analysis indicates that combining fast and slow input functions (as performed in our study) yields a reliable estimation without bias for all estimated parameters (intersection of all three in lines is around the x-value of 1, the simulated parameter value). Interestingly, Q was estimable at acceptable accuracy (which is an argument for the two-compartment carbon dioxide model that we used). Of the fixed parameters, estimation of parameters τ and V_{ALV} was poor (τ) or impossible (V_{ALV}). We relate this to the specific design of the study. A different experiment design with periods of artificial ventilation will result in estimability of V_{ALV}, while steps in carbon dioxide would have resulted in the accurate estimation of τ.

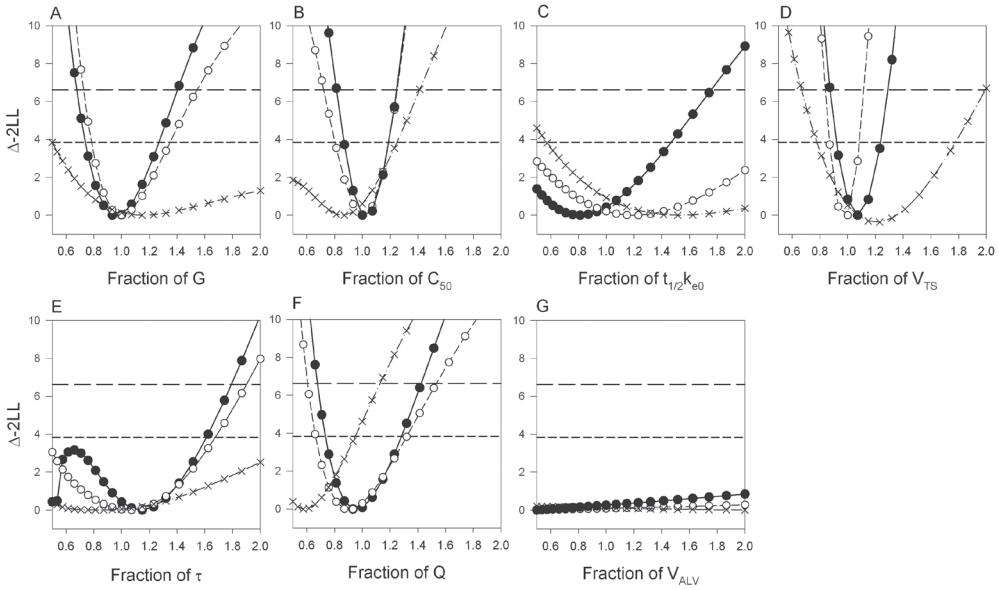

Figure 6. Sensitivity analysis for the model parameters. **A**-**D** and **F**: estimated parameters, **E** and **G**: fixed parameters. Δ–2LL is the difference in –2log likelihood between the simulated data and the best fit with one of the parameters held constant. The x-axis of each plot shows the parameter value as fraction of the value observed or fixed in the analysis of the experimental data set. The short-dashed line indicates the $P = 0.01$ level, the long-dashed line, the $P = 0.05$ level. •-• input function: step increase in plasma concentration of 1 ng.ml^{-1}, duration of step is 1 min (rate of rise = 1 ng.ml^{-1}. min^{-1}), number of steps is 5. ∘-∘ input function: step increase in remifentanil concentration is 1 ng.ml^{-1}, duration of step is 5 min (rate of rise = 0.2 ng.ml^{-1}.min^{-1}), number of steps is 5. x-x input function: step increase in plasma concentration of 1 ng.ml^{-1}, duration of step is 0.1 min (rate of rise = 10 ng.ml^{-1}.min^{-1}), number of steps is 5.

3.3.4 SIMULATION STUDY

Results of six simulations are given in Fig. 7. Linear remifentanil infusions with a rate of rise of 5 ng.ml^{-1}.min^{-1} (panels A-C), 0.5 ng.ml^{-1}.min^{-1} (panels D-F) and 0.2 ng.ml^{-1}.min^{-1} (panels G-I) are shown for the awake condition (thin line) and at the background of propofol (thick lines). The effects of the rate of rise on the nadir in ventilation (in the awake studies) and duration of apnea (in the propofol studies) are given in figure 8 for all 30 simulations. For both end-points the effect of slowing the rate-of-rise is biphasic. The nadir in ventilation decreased going from 5 to 1 ng.ml^{-1}.min^{-1} (from 2.3 to 1.6 L.min^{-1}, figure 5), after which it increased (5 ng.ml^{-1}.min^{-1}= linear infusion of 1 min; 1 ng.ml^{-1}.min^{-1} = linear infusion of 5 min). The duration of apnea increased going from 2.5 to 0.6 ng.ml^{-1}. min^{-1} (2 min and 9 min, respectively) after which it decreased rapidly. At infusion rates of 0.31 ng.ml^{-1}.min^{-1} (16 min) and slower no apnea occurred. During the two most rapid, short-term infusions (5 and 2.5 ng.ml^{-1}.min^{-1} or 1 and 2 min infusions) the remifentanil exposure was insufficient to cause apnea.

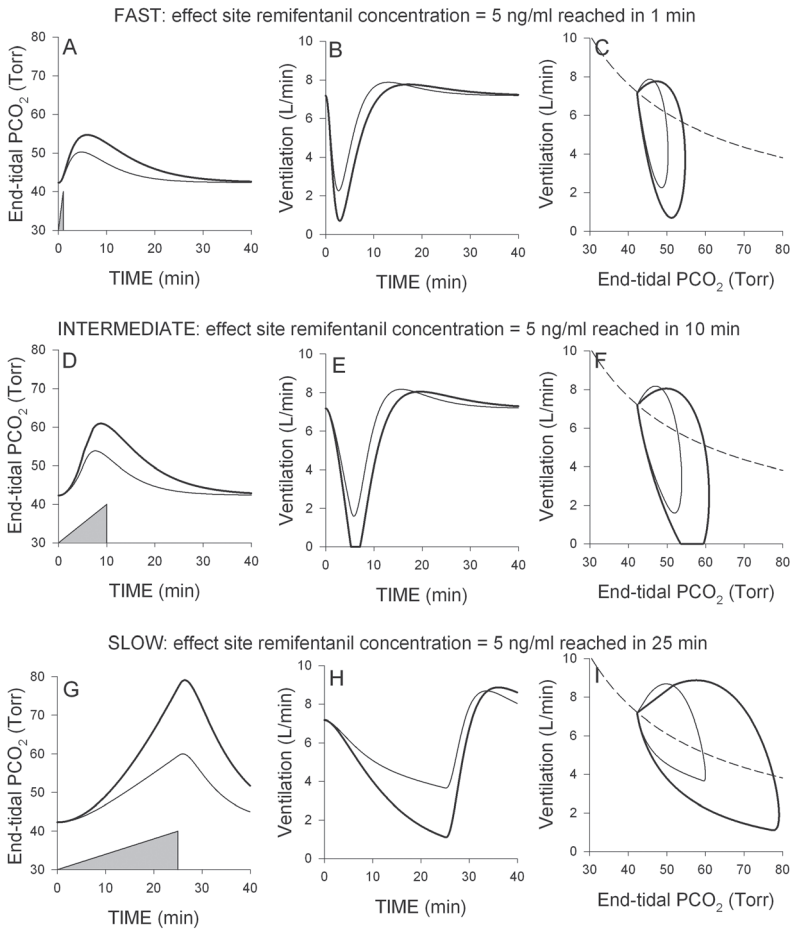

Figure 7. Simulation study on the effect of changes in the rate of rise of the effect-site remifentanil concentration on breathing (panels **A**, **D** and **G**) and end-tidal carbon dioxide concentration (panels **B**, **E** and **H**) in awake state (no propofol present, thin lines) and during sleep (due to a low-dose propofol background infusion, thick line). The remifentanil rates of rise are linear and vary from 5 $ng.ml^{-1}.min^{-1}$ given for 1 min (panels A-C) to 0.5 $ng.ml^{-1}.min^{-1}$ given for 10 min (panels D-F) and 0.2 $ng.ml^{-1}.min^{-1}$ given for 25 min (panels G-I), so that peak effect-site remifentanil concentration was 5 $ng.ml^{-1}$ in all simulations. Panels **C**, **F** and **I** depict the counter clockwise end-tidal carbon dioxide – ventilation loops (continuous lines) and metabolic hyperbola (dashed line). The gray triangles depict the linear remifentanil infusion schemes.

The carbon dioxide concentration – ventilation (counter clockwise) loops shown in Fig. 7 (panels C, F and I) are graphical representations of the link between the two parameters in areas below and above the metabolic hyperbola (dashed lines). In the simulation studies we assumed no effect of adding low dose propofol on metabolic rate (which was experimentally verified, as resting PCO_2 and minute ventilation were similar between the awake and propofol sedates states). The graphs indicate that loops in the horizontal plane (such as observed in panel I) are desirable when aiming at and maintaining spontaneous breathing. The graphs show further that independent of the infusion rate hyperventilation in the recovery phase (upswing of the loop) is greater when ventilatory depression is more pronounced and carbon dioxide accumulates in the body.
Finally, the simulations are in close agreement with the observed data; for example compare panels 7B with 5B, and 7E with 5E and 3C.

3.4 DISCUSSION

Using a 'simple' non-steady-state pharmacokinetic-pharmacodynamic model of opioid-induced respiratory depression (eqn. 6), we described the ventilatory behavior of varying remifentanil infusion schemes in awake and propofol sedated volunteers. The model is based on the linear relationship between carbon dioxide and ventilation. Most important parts of the model parameters were identifiable and estimable (*e.g.*, the drug concentration causing 50% respiratory depression, the gain factor of the respiratory controller, the remifentanil effect-site equilibration half-life), while others were fixed to values obtained from previous studies from our laboratory or obtained from the literature (the time constant for carbon dioxide of the ventilatory control system and alveolar volume). As we assumed that ventilation was dependent not only on the remifentanil concentration at its effect-site (the brainstem) but also on the metabolic product carbon dioxide, our model may be described as an indirect response model. The first (and only) previous indirect response model of opioid-induced respiratory depression was developed by Bouillon *et al*.[11,12] While their model differs at important points from ours it even so shares important characteristics. We will discuss the similarities and differences between the two models in the section 'Model Comparisons' below.

3.4.1 THE MODEL: HOW IT WORKS AND PARAMETER ESTIMATES

A schematic description of the model is given in Fig. 2. The model has three parts. The remifentanil pharmacokinetic part (part I), consisting of the distribution of remifentanil throughout the body. Part of the remifentanil passes (with a delay described by rate constant k_{e0}) to the effect site, the brainstem, where it affects the control of breathing (part II of the model via term 1 of eqn. 6: $[1 - C_{REM}/2C_{50}]$). Respiration is diminished (with time constant τ) due to activation of μ-opioid receptors expressed on key-parts of the ventilatory control system (for example, premotor neurons of the ventral respiratory group (especially within the pre-Bötzinger complex) and the pontine respiratory group).[1,2]

Part III of the model, the carbon dioxide kinetics, is affected by the diminished breathing as it reduces the efficacy of carbon dioxide output and as a consequence arterial PCO_2 increases. This again has an effect on the respiratory control system (part 2 of the model) as it stimulates breathing (via term 2 of eqn. 6: $G \cdot [P_E - P_{E\_0}]$). So, two opposing additive effects influence breathing after remifentanil infusion: the direct depressant effect *via* depression of respiratory neurons and a stimulatory effect of the increasing arterial PCO_2. In figure 9A, the effect of just term 1 of eqn. 6 is plotted (lines 1 for awake and line 3 for asleep subjects). The effect of combining terms 1 and 2 is represented by lines 2 (awake) and 3 (asleep). It is apparent from the graphs that adding term 2 has a stimulatory effect on the remifentanil-ventilation data.

An important assumption on which our model is based is that opioids (in our case remifentanil) cause a linear increase in the position of the ventilatory carbon dioxide response curve (in our model parameter B) with little change in the value of the response slope (in our model parameter G). There is ample evidence that opioids indeed cause a parallel shift of the steady-state Ventilatie-PCO_2 response slope.[10,21,22] However, some studies indicate that there is some sex dependency with a reduction in slope in women (we exclusively performed studies in men), while others showed that the opioid effect is dependent on the technique used to measure the response slope.[23] As discussed previously, we consider the parallel shift of the Ventilatie - PCO_2 response slope a typical opioid effect and reduction of the slope is in our opinion due to a lowered arousal state (from sleep or sedatives/anesthetics).[10]

The value of $t_{½}k_{e0}$ that we observed (0.5 min) is in the same range as values from Babenco *et al.* using the isohypercapnic method (2 min) and studies on electroenecephalographic end-points (1.6 min).[8] The low $t_{½}k_{e0}$ value is related to remifentanil's rapid passage across the blood-brain barrier. This rapid movement of remifentanil into the brain compartment is a potential danger, as it may produce depression of respiratory neurons (via term 1 of eqn. 6, fig 9A) before any stimulatory effect of the accumulation of carbon dioxide is generated (*via* term 2 of eqn. 6, Fig. 9A). Other opioids with a much slower passage across the blood-brain barrier (such as morphine and its active metabolite morphine-6-glucuronide with a slow passage ($t_{½}k_{e0}$ in the range of hours), but also drugs as buprenorphine (1 hour), and fentanyl (5 min)), do allow for at least some accumulation of carbon dioxide while the respiratory neurons are being depressed, hence with a lesser chance of apnea.[24-26] However, this is only true when the drug is not overdosed. Otherwise, severe respiratory depression with apnea should always be in mind.[27] Our data further indicate that the chances of apnea are increased when the subject is asleep (BIS values = 80) with propofol. When term 2 of equation 6 equals zero the remifentanil concentration causing 50% depression of ventilation is by definition C_{50} (now only term 1 of eqn. 6 is operative). This occurs in situation in which PCO_2 remains constant at baseline levels (e.g., in isohypercapnic experiments or when carbon dioxide has not yet risen above baseline values due to the rapid action of the opioid). Our C_{50} (1.6 $ng.ml^{-1}$) is therefore well

comparable to values observed in isohypercapnic studies (*cf.* Babenco *et al*.[8] who estimated a value of 1.4 ng.ml^{-1}). In a previous isohypercapnic study from our laboratory studying the remifentanil propofol interaction the C_{50} value 0.7 ng.ml^{-1} for ventilation measured at a fixed end-tidal PCO_2 of 55 Torr.[10] The observed C_{50} is a low value, probably related to a differences in parameterization (see eqn. (4) of ref. [10]) and the fact that we analyzed the whole remifentanil-propofol surface rather than just the remifentanil-ventilation relationship.

The value of G (table 2) is smaller than observed in a previous study on the effect of combining remifentanil and propofol on the ventilatory carbon dioxide response curve (value of G at $C_{REM} > 0$ = 1.6 L.min^{-1}.Torr^{-1}, see figure 1).[10] The reason for the smaller estimated value of G may be the fact that we previously tested our subjects in normoxia versus hyperoxia in the current study. Hyperoxia significantly blunts the peripheral chemoreceptors at the carotid bodies causing a 30-40% reduction of G.[15] Furthermore, we believe that the current study was performed on the dog-leg of the V - PCO_2 response slope. There is ample proof that the linear response curve flattens around resting carbon dioxide values.[14] The value observed by us is in agreement with the value presented by Babenco *et al*. following a remifentanil bolus infusion.[8] Reassuring is the observation of a 50% reduction of G by low-dose propofol, which is in agreement with earlier findings.[8]

The likelihood profile method is a tool to assess whether the parameters may be estimated from the data and also yield their 95% confidence intervals. We observed that the ability to obtain accurate parameter estimates is dependent on the specific input function chosen. Slower remifentanil infusion rates (duration 1 min or longer) resulted in more precise estimates than a rapid bolus infusion (see figure 6). This may be related to the fact that we applied a rapid infusion in just one subject while the nine others received the slower rates. However, the analysis also indicates that when applying fast and slow infusion rates in one study and analyzing the data set using a population approach, the estimation precision is acceptable and that the fast infusions do not affect the outcome of the estimates negatively.

3.4.2 SUMMARY

In summary, the estimated parameter values are in close agreement to previous reported values in the literature. This together with the results of the sensitivity analysis gives us confidence that our model adequately describes the effect of remifentanil on breathing. Furthermore, we were well able to describe and predict the occurrence of apnea.

Apnea. To the best of our knowledge there are no earlier studies that assessed remifentanil effect on apnea in healthy volunteers. The study of Egan *et al*.[28] comes closest to ours. They assessed the effect of various bolus doses of remifentanil and used a respiratory intervention scale, based primarily on SpO_2, as endpoint. Low SpO_2 values (< 85%) did occur at the higher dose range (100 μg and greater), and predominantly in a population of older subjects (60 – 75 years). The low SpO_2 values are most probably related to the

occurrence of apnea. We simulated the dosing schedule of Egan *et al.* and observed apnea at doses of 100 μg and greater (data not shown). The observation of hypoxemia is of interest. Similarly to Egan *et al.*[28] we observed hypoxia although it was mild and occurred late in the experiment (3-5 min after the start of apnea). We relate this to the inspiration of 100% oxygen in our study causing an oxygen store sufficient for 4-5 min before serious desaturation (SpO2 < 90%) sets in. Low arterial oxygen has a stimulatory effect on breathing through activation of the peripheral chemoreceptors at the carotid bodies and increases the value of G.[15,16] This may have occurred in our experiments and may have had an effect on the duration of apnea. We did not take this into account in our current model but a G dependent on SpO_2 may be introduced in future models.

Remifentanil-propofol interaction. We previously assessed the interactive effects of remifentanil (0 – 2 $ng.ml^{-1}$) and propofol (0 – 2 $\mu g.ml^{-1}$) on breathing using steady-state isohypercapnic response surface modeling techniques.[10] We observed a synergistic interaction of the two drugs on resting ventilation, resting end-tidal PCO_2, ventilation at a fixed PCO_2 of 55 Torr and the V - PCO_2 response slope. Comparison with the current data analysis is difficult due to the differences in experimental set up and modeling approach. In contrast to our previous study, we currently studied just one low propofol plasma concentration (target on average 1 $\mu g.ml^{-1}$). However, we believe (in retrospect) that the observation of large periods of apnea (1 – 7 min) during infusion of remifentanil against the background of low-dose propofol precludes testing of higher propofol doses in volunteers. The large difference in responses to remifentanil in awake and propofol-sedated states on apnea occurrence is in agreement with a synergistic interaction between the two drugs. Whether the propofol effect is related to γ-amino-butyric acidergic depression of respiratory neurons or secondary to the change in arousal-state remains unknown.[2] In agreement with the latter possibility is the finding that sleep induces a substantial enhancement of the depressant effect of morphine on ventilatory control.[29]

Speed of remifentanil infusion. It has been suggested that by slowing the opioid infusion rate the degree of respiratory depression diminishes due to the stimulatory effect of the accumulation of carbon dioxide.[3,12] We performed a simulation study to test this suggestion and observed a more complex interaction between remifentanil infusion rate and degree of depression of ventilation as measured by the nadir in ventilation (awake studies) and duration of apnea (propofol sedated studies; Fig. 7 and 8). Going from a rapid (linear) infusion (5 $ng.ml^{-1}.min^{-1}$) to a slow (linear) infusion (0.17 $ng.ml^{-1}.min^{-1}$) in target effect-site concentration (peak concentration = 5 $ng.ml^{-1}$), both endpoints showed a worsening of ventilatory depression with a lower nadir in ventilation going from 5 to 1 $ng.ml^{-1}.min^{-1}$ (infusion duration: from 1 to 5 min) and an increase in apnea duration going from 2.5 to 0.55 $ng.ml^{-1}.min^{-1}$ (infusion duration: from 2 to 9 min). Thereafter respiratory depression decreased with slowing of the infusion rate. Apnea disappeared at infusion

rates ≤ 0.31 $ng.ml^{-1}.min^{-1}$ (infusion duration = 16 min). Our analysis indicates that the degree of respiratory depression (as defined by the nadir in ventilation and duration of apnea) is related to the opioid's pharmacokinetics, the speed of opioid infusion, the total amount opioid given (at infusion durations of 1 and 2 min the total amount of remifentanil given is insufficient to cause apnea, Fig. 8), and the target plasma concentration, all relative to the carbon dioxide kinetics and dynamics. In order to prevent overt respiratory depression and apnea one should be considering all of these variables. As the simulations performed by us are not to be extrapolated to other scenarios than those applied here, a simulation for each new circumstance should be performed.

Respiratory variability. We observed great variability in the respiratory data during exposure to low-dose remifentanil (see Fig. 3 and 5). Mitsis *et al.* modeled variability of spontaneous respiration during low-dose remifentanil administration and concluded that the increase in variability due to the opioid was related to a decrease in the strength of the controller part of the ventilatory loop.[30] Our observation of a low value of G is in agreement with this statement and indeed may be the cause for the inability to strictly perform a breath-to-breath feedback control based upon the also quite varying carbon

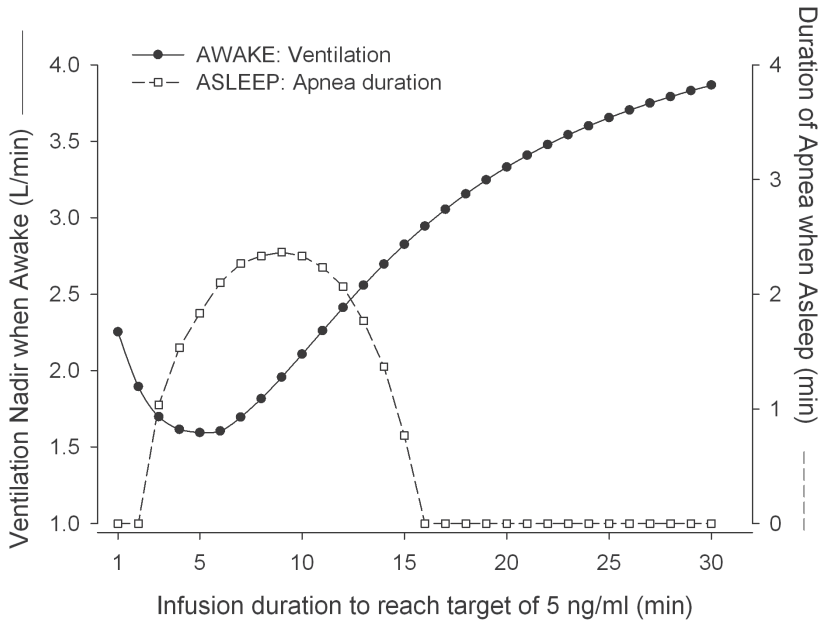

Figure 8. Simulation study on the effect of varying linear rates of rise of remifentanil effect-site concentration on the nadir in ventilation (simulations performed in the absence of propofol, closed circles) and on the duration of apnea (simulations performed in the presence of propofol, open squares).

dioxide input.

Model Comparisons. Bouillon *et al*. were the first to study and model the respiratory effects of opioids (alfentanil and remifentanil) in the non-steady state.[11,12] Their initial attempts are well appreciated and our modeling work should be considered an extension to the original ideas postulated by Bouillon *et al*.

Bouillon *et al*.[11-13] used an indirect response model consisting of two multiplicative terms, a sigmoidal Emax function and a power function of the form (eqn. 11 in ref.[12]):

$$\dot{V} = \dot{V}_0 \cdot \left[1 - \frac{C_{REM}^{\gamma}}{C_{50}^{\gamma} + C_{REM}^{\gamma}}\right] \cdot \left[\frac{P}{P_0}\right]^{F}$$

where F is the slope of the ventilatory carbon dioxide response curve (equivalent to our parameter G) and γ a shape parameter. We compared the model to our model in Fig. 9 (panel B) by plotting the acute (term 1, the sigmoid-Emax function: line 3 in Fig. 9B), and

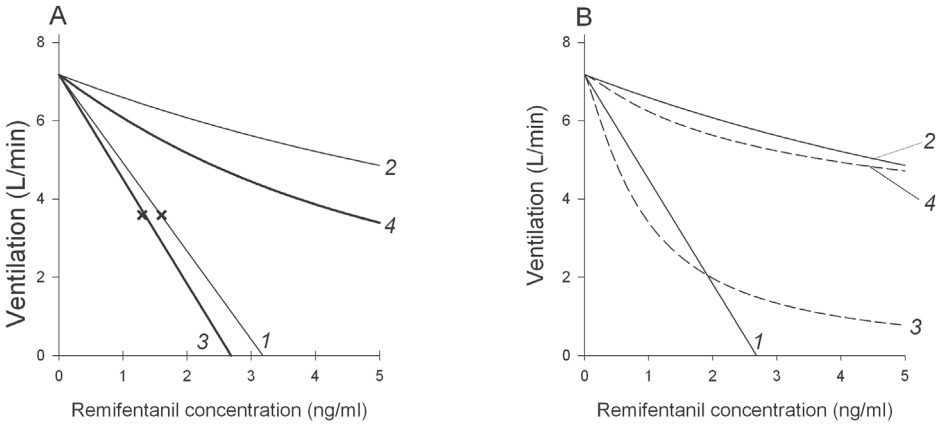

Figure 9. A. The relationship between remifentanil concentration and ventilation is made up of two additive linear terms (eqn. 6). The term that describes the effect of remifentanil on ventilation when carbon dioxide has not accumulated (the first term of eqn. 6) is given by the linear line 1 for the awake state and line 3 for the propofol sedated state. A steady state in ventilation occurs when carbon dioxide accumulates: for the awake state this is reflected by the non-linear line 2, and for the sedated state by the non-linear line 4. Now both terms of eqn. 6 are active. x are C50 values.

B. Comparison of the remifentanil – ventilation relationships derived from the model advanced by Bouillon *et al*.[12] and our model. Lines 1 and 2 are the acute (line 1) and steady-state (line 2) relationships derived from eqn. 6. Equivalent lines for the Bouillon model are lines 3 (acute relationship) and 4 (steady-state relationship) as derived from equation 14 of ref. [12.] The large difference between models is the inability to predict apnea in the latter model (line 3). The steady-state relationships are much alike (compare lines 3 and 4).

the combined (term 1 + term 2, line 4) steady-state relationships. The largest difference between the two models is the difference in the acute relationship as reflected by lines 1 and 3. Due to the sigmoidal Emax nature of term 1 and the multiplicative nature of the model, no apnea may be described or predicted. At 2 times the C_{50} the Bouillon model predicts ventilation levels > 2 $L.min^{-1}$,[12] while in our approach $2C_{50}$ equals the concentration at which apnea occurs (C_{APNEA} = 3.2 $ng.ml^{-1}$; Fig. 9). The overall steady-state relationships (lines 3 and 4) are comparable between models. In order to get an impression of the ability of the model of Bouillon *et al*.[10] to describe our data, we analyzed our data with their model. In contrast to Bouillon *et al*. we added a delay between remifentanil concentration and effect-site (parameter k_{e0}). Without this parameter no meaningful data fits were obtained. Two main observations were made: as expected, the occurrence of apnea could not be modeled but yielded systematic misfits; and the effect of manual ventilation on PCO_2 yielded misfits as well. The latter is probably related to the single carbon dioxide compartment in the Bouillon *et al*. model versus two compartments in our model. In the study of Bouillon *et al*. no systematic misfits were reported. However, this may partly be related to the remifentanil function applied (one to four 15 min steps of varying magnitudes of C_{REM}, which yielded changes towards the steady state in both PCO_2 and ventilation) together with a relatively small number of arterial carbon dioxide samples. This may have yielded little contribution of the first term of the model to the overall effect but a predominant contribution of the power function, which depends on the accumulation of carbon dioxide. Possibly at different input functions (such as bolus infusions) or during sedation, the misspecifications of the model would become apparent. Bouillon *et al*.[12] suggest to address the issue of apnea by using a logistic probability model. Our current model indicates that this is not required as apnea is accurately predicted at realistic drug concentrations. Our model has two linear terms (eqn. 6). In order to assess whether non-linear functions would improve the data fits we analyzed the data with a model consisting of power functions. No systematic improvements were observed (data not shown).

In conclusion, we developed a novel pharmacokinetic-pharmacodynamic model that is able to describe the non-steady-state effects of remifentanil on breathing under a variety of circumstances ranging from fast to slow drug infusions, under awake and sleeping conditions. Furthermore and possibly most important, the model allowed description and prediction of an important idiosyncrasy of the ventilatory control system, the development of opioid-induced apnea.

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