Pharmacokinetic–Pharmacodynamic Modeling of the Respiratory Depressant Effect of Alfentanil

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Background: Although respiratory depression is the most well-known and dangerous side effect of opioids, no pharmacokinetic–pharmacodynamic model exists for its quantitative analysis. The development of such a model was the aim of this study.

Methods: After institutional approval and informed consent were obtained, 14 men (American Society of Anesthesiologists physical status I or II; median age, 42 yr [range, 20–71 yr]; median weight, 82.5 kg [range, 68–108 kg]) were studied before they underwent major urologic surgery. An intravenous infusion of alfentanil (2.3 μg $\cdot$ kg^{-1} $\cdot$ min^{-1}) was started while the patients were breathing oxygen-enriched air (fraction of inspired oxygen [F$_{I_{O_2}}$] = 0.5) over a tightly fitting continuous positive airway pressure mask. The infusion was discontinued when a cumulative dose of 70 μg/kg had been administered, the end-expiratory partial pressure of carbon dioxide (PE$_{CO_2}$) exceeded 65 mmHg, or apneic periods lasting more than 60 s occurred. During and after the infusion, frequent arterial blood samples were drawn and analyzed for the concentration of alfentanil and the arterial carbon dioxide pressure (Pa$_{CO_2}$). A mamillary two-compartment model was fitted to the pharmacokinetic data. The Pa$_{CO_2}$ data were described by an indirect response model. The model accounted for the respiratory stimulation resulting from increasing Pa$_{CO_2}$. The model parameters were estimated using NONMEM. Simulations were performed to define the respiratory response at steady state to different alfentanil concentrations.

Results: The indirect response model adequately described the time course of the Pa$_{CO_2}$. The following pharmacodynamic parameters were estimated (population means and interindividual variability): EC$_{50}$, 60.3 μg/l (32%); the elimination rate constant of carbon dioxide (K$_{el}$), 0.088 min^{-1} (44%); and the gain in the carbon dioxide response, 4 (28%) (fixed according to literature values). Simulations revealed the pronounced role of Pa$_{CO_2}$ in maintaining alveolar ventilation in the presence of opioid.

Conclusions: The model described the data for the entire opioid–Pa$_{CO_2}$ response surface examined. Indirect response models appear to be a promising tool for the quantitative evaluation of drug-induced respiratory depression. (Key words: Indirect response model; opioids; respiratory depression.)

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RESPIRATORY depression is the most well-known and dangerous side effect of opioids. Various methods have been used in the last 30 yr to understand more fully the extent and mechanism of opioid-induced respiratory depression,[1-5] but no pharmacokinetic–pharmacodynamic model exists for its quantitative analysis. Several possible applications exist for such a model: (1) identification of patient subgroups with different sensitivity to the respiratory depressant effect of opioids; (2) determination of the reason for these differences; (3) definition of the therapeutic:toxic ratio; and (4) evaluation of opioid interactions with other drugs with regard to respiratory depression. Pharmacokinetic–pharmacodynamic modeling of opioid-induced respiratory depression differs fundamentally from modeling the electroencephalographic effects of opioids, which is well-established in the literature.[6-12] Opioids depress ventilation and thereby elevate the partial pressure of arterial carbon dioxide (Pa$_{CO_2}$). When the Pa$_{CO_2}$ is chosen as the end point, an E$_{max}$ model linking opioid concentration in the biophase

to magnitude of effect, as used in the studies noted previously, does not describe the physiologic situation, although it might be possible to fit its parameters to the data. Using an indirect effect model[13,14] accounts for the effect of opioids on the elimination of carbon dioxide rather than the Pa_{CO_2} itself. Because carbon dioxide is a strong respiratory stimulant, minute ventilation will depend not only on the current opioid concentration, but also on the current carbon dioxide tension (P_{CO_2} within the respiratory center, which can be approximated using the Pa_{CO_2}. This apparent tolerance development must be accounted for in the model.

The aim of the study was the development of a pharmacokinetic–pharmacodynamic model for opioid-induced respiratory depression with the following features: (1) Carbon dioxide is treated as an endogenous metabolite that possesses its own kinetic properties. (2) Carbon dioxide elimination is impeded by the opioid, depending on the opioid concentration. (3) Increasing carbon dioxide concentrations stimulate carbon dioxide elimination.

Materials and Methods

Participants

After we obtained institutional review board approval and written informed consent, we studied 14 men classified as American Society of Anesthesiologists physical status I or II who were undergoing major urologic surgery. Their median age was 42 yr (range, 19–72 yr) and their median weight was 82.5 kg (range, 68–108 kg).

Study Design

The unpremedicated patients were studied before anesthesia was induced. After arrival in the induction room, standard monitoring (noninvasive blood pressure, electrocardiography, and pulse oximetry) devices were placed. Two intravenous (both forearms) and one arterial cannula (radial artery of the nondominant hand) were inserted. An intravenous infusion of alfentanil (2.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was started while the patients were breathing oxygen-enriched air (Fi_{O_2} = 0.5) over a tightly fitting continuous positive airway pressure mask. This enabled us to obtain respiratory rate, approximate minute ventilation, and end-expiratory partial pressure of carbon dioxide (Pe_{CO_2}) using the standard monitors of an anesthesia workstation (Cicero; Draeger, Luebeck, Germany). The infusion was discontinued when a cumulative dose of 70 $\mu g/kg$ was given, Pe_{CO_2} exceeded 65

mmHg, or apneic periods lasting more than 60 s occurred. Based on pharmacokinetic simulations, the cumulative dose was chosen to yield concentrations between 200 and 250 $\mu g/l$, which were identified as allowing adequate spontaneous ventilation during recovery from anesthesia.[15] During the study, an observational scale (1 = awake, restless; 2 = awake, calm; 3 = lightly sedated; 4 = asleep) and continuous electroencephalographic monitoring were used to assess the patients' state of arousal. The study was discontinued at any time when verbal stimulation was required to maintain spontaneous ventilation or the patients were uncomfortable while breathing through the mask. Otherwise data were collected for 60 min after the infusion began. Anesthesia was induced immediately after the study was discontinued.

Sample Handling and Processing

Arterial blood samples were drawn before and 3, 6, 9, 12, 15, 20, 25, 30, 35, 40, 45, 50, and 60 min after the start of the infusion for alfentanil assay and determination of the Pa_{CO_2}.

All samples were stored on ice after collection. Before the study, we ensured that storing the arterial blood samples on ice for as long as 2 h in the tubes used for the study did not lead to appreciable changes of the Pa_{CO_2}. We did this in response to several published reports regarding this issue.[16–20] We performed blood gas analyses immediately after the study was discontinued using an automated analyzer with an autocalibration function (ABL 505; Radiometer Medical A/S, Copenhagen, Denmark). The blood samples drawn to analyze the alfentanil concentration were centrifuged at 3,000 rpm for 15 min and the plasma was stored at $-20°C$ until the assay.

Analysis of Alfentanil

Alfentanil concentrations were determined using a sensitive and selective high-performance liquid chromatography assay. Briefly, alfentanil and sufentanil (Janssen, Beerse, Belgium), the latter serving as an internal standard, were extracted from the plasma samples as previously described.[21] The recovery rate was 89%. The samples were analyzed by high-performance liquid chromatography (mobile phase: 0.03 M NaH_2PO_4, 55%; acetonitrile, 35%; isopropanol, 10%; column: Supelcosil DB-8 [250 × 4.6 mm] with ultraviolet detection [220 nm]). Retention times were 5.4 min for alfentanil and 8.8 min for sufentanil. The limit of quantitation was 10 $\mu g/l$. The assay was linear in a concentration range of 10–

1,000 μg/l (coefficient of correlation = 0.991). Precision of the assay was 2.95% (coefficient of variation).

Pharmacokinetic-Dynamic Analysis

The program system NONMEM, version IV with the First Order Conditional Estimation method and η-ϵ interaction to reduce the influence of model misspecification was used for all model fits, empirical Bayesian estimation of the individual parameters, and simulations.[22]

The pharmacokinetic-dynamic analysis was performed sequentially. The population means, the interindividual variability, and the empirical Bayesian estimates of the individual pharmacokinetic parameters were determined first. Subsequently, the pharmacodynamic data (Pa_{CO_2}) were analyzed with fixed individual pharmacokinetic parameters.

An exponential model was used to describe the interindividual variability in the pharmacokinetic and the pharmacodynamic parameters:

$$\theta_{(n,i)} = \theta_{(n,m)} \cdot e^{\eta(i)} \qquad (1)$$

where $\theta_{(n,i)}$ refers to the individual value of the nth parameter in the ith individual, $\theta_{(n,m)}$ is the typical value in the population of the nth parameter, and η varies randomly among individuals with a mean of zero and a diagonal variance-covariance matrix Ω^2.

A multiplicative (constant CV) error model was chosen to model residual variability:

$$DV_{obs} = DV_{exp} \cdot (1 + \epsilon) \qquad (2)$$

DV_{obs} refers to the observed value of the dependent variable (alfentanil concentration, Pa_{CO_2}), and DV_{exp} refers to the value predicted based on dose, time, and the individual pharmacokinetic and pharmacodynamic parameters. ϵ is a normally distributed random variable with mean zero and variance σ^2.

Decisions between different models were made using the Akaike information criterion.[23] We checked for model misspecification by plotting the ratio of the measured and the predicted concentrations against time on a semilogarithmic scale. The covariates tested were weight, age, and completion of the infusion. Covariates were included in the model if the inclusion significantly improved the log likelihood criterion ($P < 0.01$).[22]

Pharmacokinetic Analysis

One-, two-, and three-compartment models were fitted and compared as described before. The models were parameterized in terms of the volumes of distribution, the elimination clearance, and the intercompartmental (distribution) clearances.

Pharmacodynamic Analysis

Because of the direct relation between the volume of a gas and its molar weight (22.4 l of an ideal gas [22.2 l carbon dioxide] equals 1 mol during standard temperature pressure dry conditions[24]), mass balance equations can be used to describe volume changes. Constant temperature, volumes, and pressures are directly proportional; therefore, changes of partial pressures of a gas also can be computed by mass balance equations. The most simplistic model of carbon dioxide turnover in the body would be a one-compartment model with constant input (carbon dioxide production) and constant output (carbon dioxide elimination) during baseline steady state conditions. The "concentration" in the compartment equals the Pa_{CO_2} normalized to atmospheric pressure in our model.

$$\frac{d}{dt} V_d CO_2 \cdot \frac{Pa_{CO_2}}{760} = k_{in}(t) - k_{out}(t) \qquad (3)$$

where $V_d CO_2$ is apparent volume of distribution of carbon dioxide in the body (in l); Pa_{CO_2} is arterial partial pressure of carbon dioxide (in mmHg); k_{in} is production rate of carbon dioxide (in l/min); k_{out} is elimination rate of carbon dioxide (in l/min); 760 is atmospheric pressure at sea level (in mmHg); $k_{out}(t)$ is the product of the (pulmonary) clearance (Cl; in l/min) and the Pa_{CO_2} at time t divided by the barometric pressure.

$$\frac{d}{dt} V_d CO_2 \cdot \frac{Pa_{CO_2}}{760} = k_{in}(t) - Cl \cdot \frac{Pa_{CO_2}(t)}{760} \qquad (4)$$

Considering that the difference between Pe_{CO_2} and alveolar carbon dioxide pressure (PA_{CO_2}) is small in healthy persons, clearance of carbon dioxide can be substituted by alveolar ventilation (V_{alv}).

$$\frac{d}{dt} V_d CO_2 \cdot \frac{Pa_{CO_2}}{760} = k_{in}(t) - \dot{V}_{alv} \cdot \frac{Pa_{CO_2}(t)}{760} \qquad (5)$$

During baseline steady state conditions (at t = 0), before drug exposure:

$$\frac{d}{dt} V_d CO_2 \cdot \frac{Pa_{CO_2}}{760} = 0 \qquad (6)$$

And therefore

$$k_{in}(0) = \dot{V}_{alv}(0) \cdot \frac{Pa_{CO_2}(0)}{760} \qquad (7)$$

Under the assumption that carbon dioxide production remains constant, $k_{in}(t)$ can be expressed as the product of the baseline value of the normalized Pa_{CO_2} and alveolar ventilation.

$$\frac{d}{dt} V_d CO_2 \cdot \frac{Pa_{CO_2}}{760} = \dot{V}_{alv}(0) \cdot \frac{Pa_{CO_2}(0)}{760}$$
$$- \dot{V}_{alv}(t) \cdot \frac{Pa_{CO_2}(t)}{760} \qquad (8)$$

Rearranging for the change of Pa_{CO_2}, the dependent variable, over time yields

$$\frac{d}{dt} Pa_{CO_2} = \frac{\dot{V}_{alv}(0)}{V_d CO_2} \cdot Pa_{CO_2}(0) - \frac{\dot{V}_{alv}(t)}{V_d CO_2} \cdot Pa_{CO_2}(t) \qquad (9)$$

Alternatively, the ratio of the alveolar ventilation and the apparent volume of distribution of carbon dioxide can be expressed as the elimination constant of carbon dioxide, k_{el} (min^{-1}).

$$\frac{d}{dt} Pa_{CO_2} = k_{el}(0) \cdot Pa_{CO_2}(0) - k_{el}(t) \cdot Pa_{CO_2}(t) \qquad (10)$$

The equation must be completed for the respiratory depressant effect of opioids and the respiratory stimulant effect of carbon dioxide. Because the volume of distribution remains constant, all changes in carbon dioxide elimination must be caused by changes of V_{alv}. Opioids are known to reduce (alveolar) ventilation.[25] Because the change in Pa_{CO_2} is not a direct effect of opioids but rather is an indirect effect after the reduction of alveolar ventilation caused by opioids, we chose to model the relation between alfentanil concentration and Pa_{CO_2} using an indirect-response model.[13,14] A linear model with a negative slope and a fractional E_{max} model were tested.

$$\dot{V}_{alv}(c) = \dot{V}_{alv}(0) \cdot (1 - n \cdot c(t)) \qquad (11)$$

$$\dot{V}_{alv}(c) = \dot{V}_{alv}(0) \cdot \left(1 - \frac{c(t)}{EC_{50} + c(t)}\right) \qquad (12)$$

with c referring to the current opioid concentration, n referring to the slope factor, and EC_{50} referring to the concentration at which V_{alv}, and therefore k_{el}, would be decreased to 50% of the value in the absence of opioid.

To avoid redundancy, the further derivations are shown for the fractional E_{max} model only.

Carbon dioxide is a powerful respiratory stimulant.[1] Its response curves are shaped like a hockey stick,[1,24] which is usually described in terms of a carbon dioxide threshold and the linear slope of the carbon dioxide response curve. The following hyperbolic function displays a similar shape and predicts a continuous, nonlinear decrease of the ventilation at less than a physiologic Pa_{CO_2}, which corresponds with a study that evaluated the respiratory rate and inspiratory effort during hypocapnic and hyperoxic conditions in awake volunteers.[26]

$$\dot{V}_{alv}(Pa_{CO_2}) = \dot{V}_{alv}(0) \cdot \left(\frac{Pa_{CO_2}(t)}{Pa_{CO_2}(0)}\right)^F \qquad (13)$$

F denotes the gain of the system. Equations 12 and 13 can be combined to describe the net effect for any given opioid concentration and Pa_{CO_2} on alveolar ventilation as the product of the terms. This is depicted in figure 1.

$$\dot{V}_{alv}(c, Pa_{CO_2}) = \dot{V}_{alv}(0) \cdot$$
$$\left(1 - \frac{c(t)}{EC_{50} + c(t)}\right) \cdot \left(\frac{Pa_{CO_2}(t)}{Pa_{CO_2}(0)}\right)^F \qquad (14)$$

Note that an opioid concentration equal to the EC_{50} only leads to a 50% reduction in V_{alv} if the output of the second term equals 1.

Combining equations 14 and 9 yields the final equation to describe opioid-induced hypercapnia.

$$\frac{d}{dt} Pa_{CO_2} = \frac{\dot{V}_{alv}(0)}{V_d CO_2} \cdot Pa_{CO_2}(0) - \frac{\dot{V}_{alv}(0)}{V_d CO_2} \cdot$$
$$\left(1 - \frac{c(t)}{EC_{50} + c(t)}\right) \cdot \left(\frac{Pa_{CO_2}(t)}{Pa_{CO_2}(0)}\right)^F \cdot Pa_{CO_2}(t) \qquad (15)$$

Simulations

A combined pharmacokinetic–pharmacodynamic simulation of the hypercapnic effect of alfentanil was performed for a population of 100 participants during an intravenous infusion of 5.78 mg in 30 min, the calculated dose for the median participant (Wt = 82.5 kg). One hundred sets of individual pharmacokinetic and pharmacodynamic parameters were simulated based on the estimated population means and interindividual variances.

Further simulations were performed to obtain estimates of the steady state Pa_{CO_2}, corresponding to several alfentanil concentrations (50, 100, 150, 200, and 250 $\mu g/l$). Baseline alveolar ventilation was not measured, so

we cannot calculate absolute alveolar ventilation. However, because any change of k_{el} must be attributed to a change in V_{alv}, the relative change of alveolar ventilation can be calculated as shown below to obtain steady state alveolar ventilation normalized to baseline during different opioid concentrations.

$$\frac{V_{alv}(c_{ss}, \; Pa_{CO_2}(c_{ss}))}{V_{alv}(0)} =$$

$$\left(1 - \frac{c_{ss}}{EC_{50} + c_{ss}}\right) \cdot \left(\frac{Pa_{CO_2}(c_{ss})}{Pa_{CO_2}(0)}\right)^F \quad (16)$$

The subscript "ss" refers to steady state. Alveolar ventilation normalized to baseline is now called "fractional alveolar ventilation."

Results

General

In 6 of 14 patients studied, the infusion had to be discontinued prematurely. Three experienced apneic periods lasting more than 60 s, and the other three reached an PE_{CO_2} more than 65 mmHg. In three patients, the data collection had to be discontinued prematurely: one needed verbal stimulation to continue breathing after 20 min of drug administration and two patients were uncomfortable and nauseated while they breathed through the mask after 45 min. They received 1.25 mg droperidol as an intravenous bolus to treat nausea, both after 46 min. One patient received 10 mg intravenous urapidil, a substance with α_1-antagonistic and α_2-agonistic properties, to treat hypertension after 17 min. No

Table 1. Pharmacokinetic Parameters of Alfentanil Describing the Concentration Time Data over the Study Period (60 min)

Estimated Parameters	Population Mean (% CV)
Volumes [l]	
Central (V_1)	5.35 (26)
Peripheral (V_2)	10.4 (—)
Clearances [l/min]	
Central (Cl_1)	0.35 (42)
Peripheral (Cl_2)	0.54 (53)

The estimated parameters are those characterized by the mixed effects model using the computer program NONMEM. The percent coefficient of variation is the square root of the variance of η and thus only approximates the CV in the usual sense. To obtain the true, asymmetric 16–84% quartile, divide/multiply the respective population mean by/with $e^{\sqrt{\omega^2}}$. The mean residual error was 34.4% without and 16.5% with accounting for interindividual variability. Standard errors were 11–21% for the structural and 44–77% for the variance parameters.
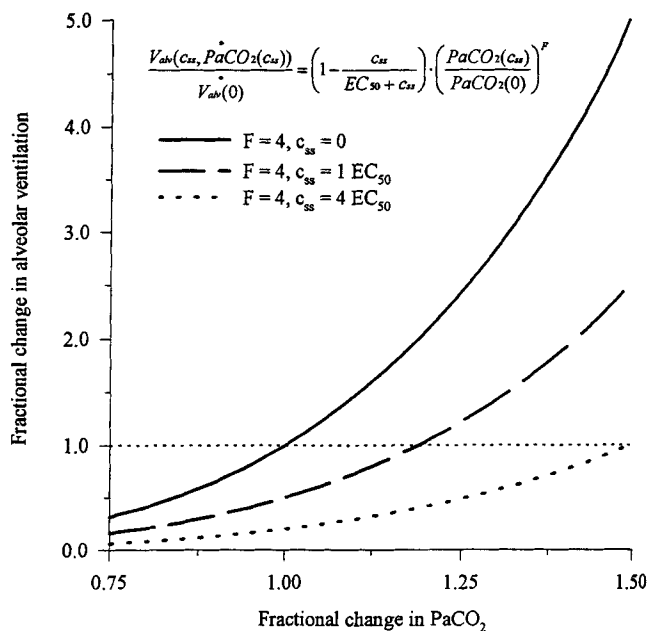
Fig. 1. The gain in alveolar ventilation in response to the partial pressure of carbon dioxide in arterial blood (Pa_{CO_2}) in the presence of different concentrations of opioid expressed as multiples of the EC_{50}. Alveolar ventilation and Pa_{CO_2} are divided by their respective baseline values. The gain in the carbon dioxide response curve has been fixed according to data published in the literature, as noted in Materials and Methods.

patient was more than lightly sedated, as judged from clinical observation and electroencephalographic data.

Pharmacokinetics

The concentration time course of alfentanil in 60 min was adequately described by a two-compartment model. Table 1 shows the pharmacokinetic parameters. Figures 2A and B show the goodness of fit under the population model and using the Bayesian estimates of the individual pharmacokinetic parameters. As shown in figure 2C, the population means and variability parameters of the mixed-effects model were used to simulate a population of 100 persons receiving the median cumulative dose (5.78 mg in 30 min). The actual measured concentration–time data are superimposed on the simulations. The data from persons who did not receive the full dose are included up to the discontinuation of the infusion. We must stress that all concentration–time courses are predicted well with Bayesian estimates of the pharmacokinetic parameters (fig. 2B), because these were used to generate the concentration–time profiles that provided the input for the pharmacodynamic model.
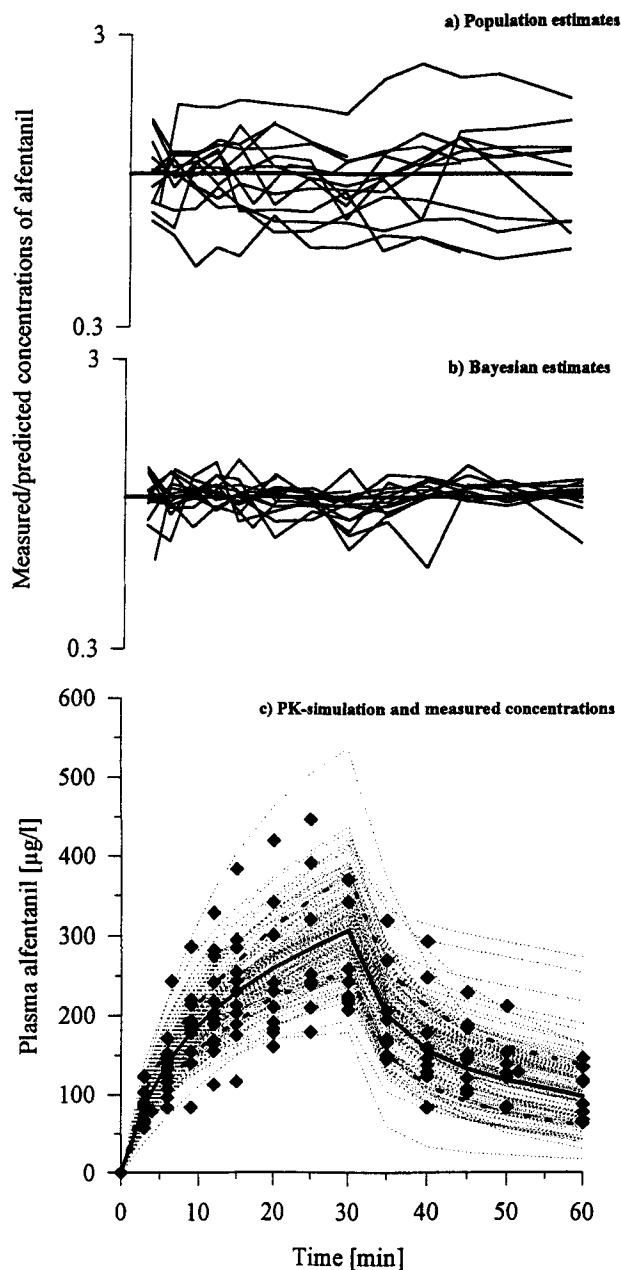
Fig. 2. The measured and predicted alfentanil concentrations *versus* time. The line drawn at y = 1 represents a perfect prediction. (*A*) The predictions are based on mean pharmacokinetic parameters and the individual dosing histories. (*B*) Predictions are based on Bayesian estimates of the individual pharmacokinetic parameters and the individual dosing histories. (*C*) A model-based simulation of the plasma concentration time course of alfentanil during and after an infusion of 5.78 mg (median cumulative dose) in 30 min. The population mean (–), the 16 and 84% quartiles (- - -), and the individual concentration time courses (. . .) (n = 100) are displayed. The actual measured concentrations are superimposed (♦). The measured concentrations of patients in whom the infusion was prematurely discontinued are included up to their stopping times.
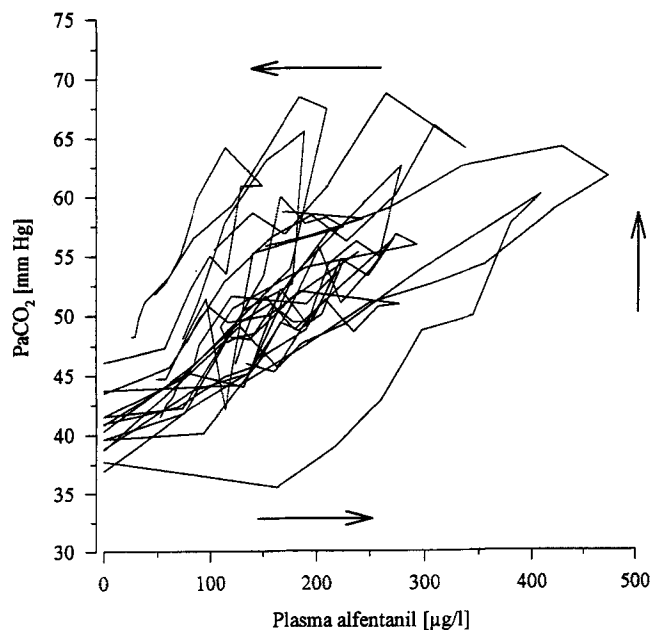

Fig. 3. The measured partial pressure of carbon dioxide in arterial blood (Pa_{CO_2}) *versus* Bayesian estimates of the alfentanil plasma concentration. Note the counterclockwise hysteresis.

Pharmacodynamics

Figure 3 depicts the relation between plasma concentrations predicted by dose, time, and the Bayesian estimates of the individual pharmacokinetic parameters and the measured Pa_{CO_2} concentrations. A counterclockwise hysteresis can be observed.

Both by inspection of the residuals and by the Akaike information criterion, the fractional E_{max} model was found to be superior to the negative-slope model for describing the respiratory depressant effect of alfentanil. Table 2 shows the pharmacodynamic parameters of the E_{max} model. Because we could not simultaneously estimate F and EC_{50}, the population mean of F was fixed, as indicated in Materials and Methods. The interindividual variability of F was estimated using the model. There was a trend toward lower values of F in the *post hoc* estimates of the six patients in whom the infusion was discontinued prematurely, which was not statistically significant. Figure 4A shows the goodness of fit under the population model, and figure 4B shows the goodness of fit using the Bayesian estimates of the individual pharmacodynamic parameters. In figure 4C, the population means and variability parameters of the mixed-effects model were used to simulate a population of 100 persons who received the median cumulative dose (5.78 mg in 30 min). The measured Pa_{CO_2} data are superimposed on the simulation. The data from persons who did not

Table 2. Pharmacodynamic Parameters

Parameter	Population Mean (% CV)
k_{el} (min^{-1})	0.088 (44)
EC_{50} (μg/l)	60.3 (32)
F(—)	4.0 (28)

The estimated parameters are those characterized by the mixed effects model using the computer program NONMEM. The population mean of F was fixed according to literature data as indicated in Methods. The percent coefficient of variation is the square root of the variance of η and thus only approximates the CV in the usual sense. To obtain the true, asymmetric 16–84% quartile, divide/multiply the respective population mean by/with $e^{\sqrt{\omega^2}}$. The mean residual error was 7.9% without and 4.7% with accounting for interindividual variability. Standard errors were 17 and 20% for the structural and 57–97% for the variance parameters.

receive the full dose are included until the infusion was stopped.

Figure 5A shows the predicted steady state relation between alfentanil concentration and Pa_{CO_2}, and figure 5B shows the corresponding fractional alveolar ventilation calculated as indicated in Materials and Methods. One hundred subjects per concentration were simulated. Displayed are the individual values, the median, and the 16 and 84% quartiles of the distribution for steady state concentrations within the range of the concentrations observed during the study. The median values are also summarized in table 3.

Figures 6A and B show the relation of fractional alveolar ventilation, Pa_{CO_2}, and opioid concentration for the mean participant. In figure 6A, the mean response surface, all data points obtained (dots), and the calculated mean steady state ventilation (bold line) are displayed. In figure 6B, the mean response surface has been shaded and the individual data and steady state response are omitted.

Discussion

Pharmacokinetics

The goal of this study was to provide a model-based description of the time course of opioid-induced respiratory depression. Therefore, we did not obtain blood samples after the pharmacodynamic measurements were made. The pharmacokinetic model merely serves as the input for the pharmacodynamic model during the Pa_{CO_2} measurements. The parameters cannot be used to extrapolate the concentration time course of alfentanil beyond the study period.

Pharmacodynamics

The following aspects must be considered when modeling opioid-induced respiratory depression: the end point assessed, the design of the study, and the modeling approach used. The effects of opioids on ventilation are classically described using carbon dioxide response curves.[1-3] We decided against this approach for three reasons. First, because recording a single carbon dioxide response curve takes minutes, the drug concentration at the effect site must be held steady. This can be achieved with computer-controlled drug delivery but limits the number of concentrations that can be assessed. Second, carbon dioxide response curves require the administration or rebreathing of carbon dioxide, which must be allowed to wash out before a new measurement can be obtained. By allowing one measurement every 15 min,[3] this severely limited the resolution of the method. Although this design was used by Hill *et al.*[27] to compare the respiratory depressant action of opioids with considerable success, it does not provide sufficient points on the concentration-effect curve for a modeling approach. Furthermore, steady state data are not helpful when trying to characterize the behavior of the system in a non-steady state situation, which is commonly encountered in the clinical setting. For the latter reason, our goal was to perform a non-steady state analysis. Third, the clinical significance of the parameters obtained is difficult to assess. Clinicians will be considerably more interested in the opioid concentration that increases the Pa_{CO_2} or that decreases alveolar ventilation to a certain value than in the concentration that decreases the slope of the carbon dioxide response curve by some percentage. Exactly the same problems will be encountered when measuring the opioid-induced attenuation of the hypoxic respiratory drive. For these reasons, carbon dioxide-oxygen response curves were excluded *a priori* as a primary end point. Minute ventilation is influenced by Pa_{CO_2} and opioid concentration, as can be seen from carbon dioxide response curves under different opioid concentrations. The same is true for alveolar ventilation. Therefore, modeling the influence of an opioid on minute or alveolar ventilation without concomitantly measuring and modeling Pa_{CO_2} or PE_{CO_2} will lead to a biased estimate for the potency of the opioid. Because the respiratory stimulant effect of carbon dioxide would be missed, falsely high estimates of the EC_{50} would be obtained. Even worse, because different input functions of the opioid, most notably bolus *versus* slow infusion, would lead to different time courses of Pa_{CO_2}, which would not be accounted for in
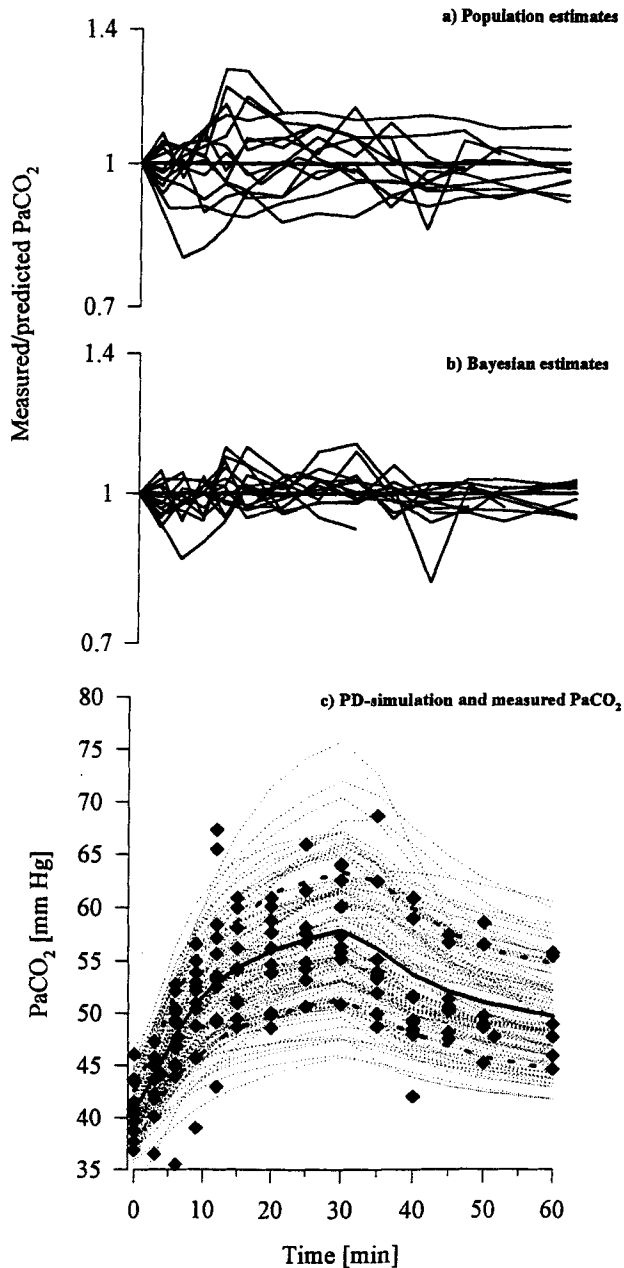
Fig. 4. Measured and predicted partial pressures of carbon dioxide in the arterial blood (Pa_{CO_2}) *versus* time. The line drawn at y = 1 represents a perfect prediction. The prediction in the absence of drug is defined in the model as the measured concentration of the respective patient (= fixed baseline). (A) The predictions are based on the individual dosing histories, the Bayesian predictions of the pharmacokinetic parameters, and the mean pharmacodynamic parameters. (B) The predictions are based on the individual dosing histories and the Bayesian predictions of the individual pharmacokinetic and pharmacodynamic parameters. (C) A model-based simulation of the Pa_{CO_2} in the study population during and after an alfentanil infusion of 5.78 mg (median cumulative dose) in 30 min. The population
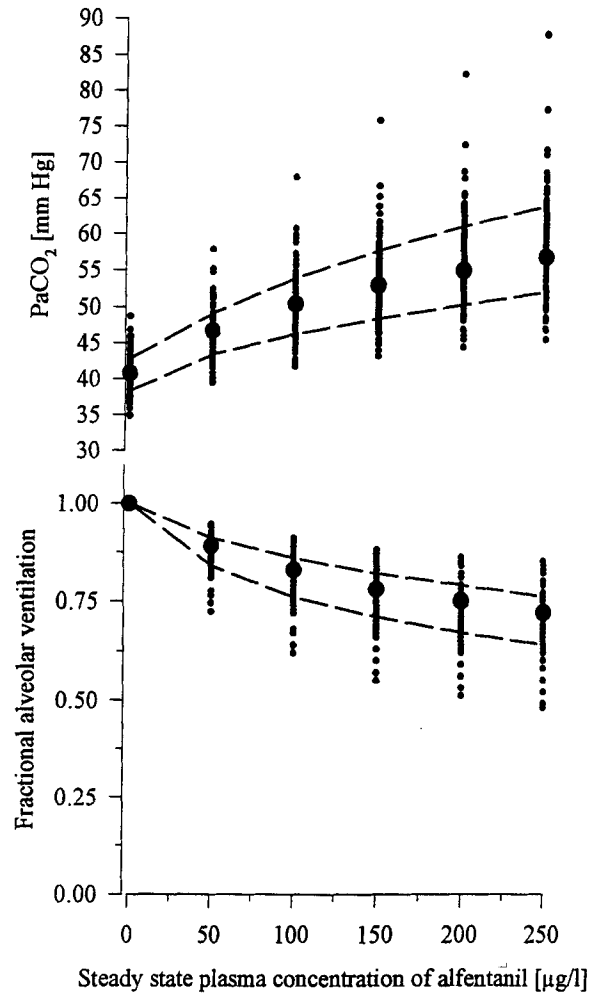

Steady state plasma concentration of alfentanil [µg/l]

Fig. 5. (*Top*) Predicted partial pressures of carbon dioxide in arterial blood (Pa_{CO_2}) and (*bottom*) fractional alveolar ventilation for different alfentanil concentrations at steady state. Predictions are confined to the range covered by measurements. Simulations were performed for 100 persons per concentration (•). The median expected Pa_{CO_2} (●) and the 16 and 84% quartiles (- - -) are also shown.

the model, the estimate of the EC_{50} might become dependent on the experimental design. These systematic errors might occur even in the presence of an adequate fit for the data measured.

The Pa_{CO_2} is easily measured; the measurements can be

mean (–), the 16% and 84% quartiles (- - -), and the individual concentration time courses (...) (n = 100) are displayed. The actual measured Pa_{CO_2} values are superimposed (♦). The measured Pa_{CO_2} values of patients in whom the infusion was prematurely discontinued are included up to the respective stopping times.

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Table 3. Median Predictions for Pa_{CO_2} and the Fractional Alveolar Ventilation under Steady State Conditions

C_{pss} Alfentanil ($\mu g/l$)	$Pa_{CO_2 ss}$ (mmHg)	$V_{alv\ ss}/V_{alv}(0)$ (—)
0	40.8	1.00
50	46.7	0.89
100	50.4	0.83
150	52.9	0.78
200	54.9	0.75
250	56.7	0.72

The steady state ventilation can was calculated as described in Methods. The subscript "ss" refers to steady state.

taken in short intervals (minutes); and it is highly clinically significant. Therefore, we chose Pa_{CO_2} as our pharmacodynamic end point. To achieve a gradually increasing degree of respiratory depression and pronounced hypercapnia without encountering respiratory arrest, we decided to administer the drug by zero-order infusion. We aimed for a target concentration between 200 and 250 $\mu g/l$, which was previously determined to allow adequate spontaneous ventilation after surgery.[15] Although the infusion was discontinued prematurely in 6 of 14 patients, only one patient was prematurely lost to data acquisition because of pronounced respiratory depression. Conversely, nearly every patient showed pronounced hypercapnia (fig. 4C). We believe the goal of obtaining a sufficient range of the Pa_{CO_2} without compromising patient safety has been adequately achieved.

As stated in Materials and Methods, the relation between alfentanil concentration and Pa_{CO_2} is indirect. As expected, a modified indirect-response model adequately described the data. Although effect compartment concentrations had to be calculated to model the electroencephalographic slowing effect of alfentanil,[6] alfentanil-induced respiratory depression could be modeled assuming a direct relation between plasma concentrations and effect. Because the plasma effect compartment equilibration half-time of alfentanil is 1.1 min, much smaller than the 5 min required for a 50% change in the Pa_{CO_2} from the current to the new steady state level after a change of alveolar ventilation,[28] the k_{eo} of alfentanil could not be estimated from our data. The hysteresis displayed in figure 3 was explained entirely by the inherent inertia of the indirect effect model. However, failure to account for the equilibration of alfentanil with the effect site could have distorted the estimate of the elimination constant of carbon dioxide (k_{el}). Because the product of k_{el} and the baseline value of Pa_{CO_2} ($Pa_{CO_2}(0)$), yields the fastest possible increase of Pa_{CO_2} according to the model, it can be used to check for

plausibility. The model predicts a maximal rate of 3.6 mmHg/min, which agrees closely with the value published in a standard text of respiratory physiology (3–6 mmHg/min).[24]

Because we could assign a physiologic meaning to the elimination constant of the indirect response model (the ratio of alveolar ventilation and the volume of distribution of carbon dioxide), we could predict changes in alveolar ventilation using parameters estimated solely from fitting Pa_{CO_2} data. Because patients with opioid-induced respiratory depression are more likely to have complications from hypoxemia than from hypercapnia, this feature of the model is especially attractive.

The following potential shortcomings of our approach must be considered. First, as can be seen in the derivation of the model, the production rate of carbon dioxide has been substituted by the product of the elimination rate and Pa_{CO_2} in the absence of drug, which is equal to the assumption that carbon dioxide production remains constant during the entire study. In a recent study, carbon dioxide production was diminished 12–19% from baseline during a target-controlled infusion of alfentanil to 40 $\mu g/l$,[29] a very low concentration compared with the 300 $\mu g/l$ observed in some patients in our study. However, there is clear evidence that this trend does not continue. Hill *et al.*[27] measured carbon dioxide production of healthy volunteers at a steady state alfentanil concentration of 80 $\mu g/l$ and found no significant difference from baseline. Weyland *et al.*[30] compared oxygen consumption during sedation with midazolam, propofol, thiopental, and fentanyl. All hypnotics reduced oxygen consumption by as much as 15% from baseline. Patients receiving fentanyl exhibited a slight (5%) but not significant increase in oxygen consumption, at a Pe_{CO_2} of 50 mmHg, when compared with placebo. Interestingly, these patients were only lightly sedated at this degree of respiratory depression, which corroborates our findings that profound opioid-induced respiratory depression is not accompanied by substantial sedation or sleep.

Assuming a constant carbon dioxide production during the course of the study cannot be considered a relevant systematic error. Nevertheless, by introducing several pseudo–steady state steps with a computer-controlled infusion and measuring carbon dioxide production before drug administration and during pseudo–steady state, this potential pitfall could be avoided completely.

Second, because we could not simultaneously fit the population means of both the EC_{50} and F, the gain of the carbon dioxide response curve, we had to fix the mean
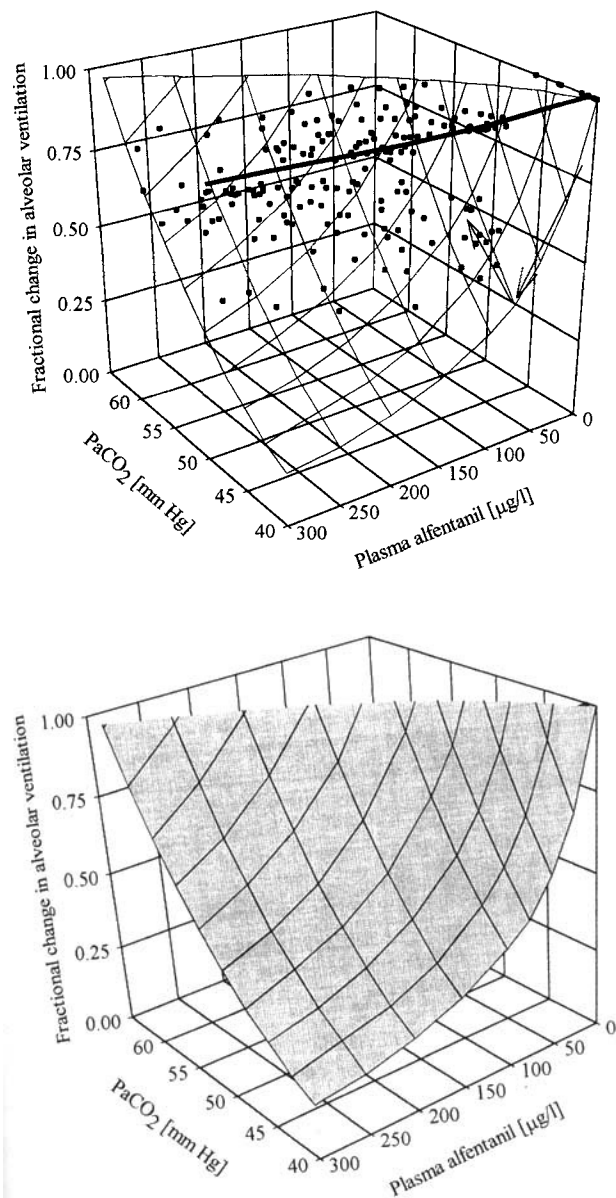
Fig. 6. (*Top*) The relation among plasma alfentanil concentration, the partial pressure of carbon dioxide in arterial blood (Pa_{CO_2}), and fractional alveolar ventilation. The plane refers to the population mean of the pharmacodynamic parameters. The predicted steady state ventilation for different opioid concentrations (–) and the actual data (●) are also shown. Note the nearly empty area at a low Pa_{CO_2} and high opioid concentrations (no measurements could be obtained if apneic periods were to be avoided). Also note the relatively high values for alveolar ventilation despite high alfentanil concentrations, if the Pa_{CO_2} is sufficiently high. The arrows indicate the order of events after a sudden increase and subsequent maintenance of the opioid concentration. First, alveolar ventilation will decrease, followed by an increase in Pa_{CO_2}, and finally, because of the respiratory stimulant effect of carbon dioxide, an increase in the alveolar ventilation until a new steady state is reached. (*Bottom*) The same relation as shown in the *top panel*

response to carbon dioxide in the population to a predetermined value. Because we estimated the interindividual variability in the population, we were able to individualize the gain of the carbon dioxide response curve. This technique, assigning a mean response and estimating the magnitude of the interindividual variability, can be used only with a population approach. However, measurement of a single carbon dioxide response curve in the absence of opioid in every patient before the study would have directly provided information about the individual sensitivity to carbon dioxide, which could have been exploited in the modeling approach. This fact should be accounted for in future designs.

Third, our modeling approach considers the body as a single compartment, with a partial pressure of carbon dioxide equaling Pa_{CO_2}. Because it is obvious that the Pa_{CO_2} and central venous partial pressures of carbon dioxide differ, this simplification contradicts existing knowledge of physiology. The derivation of a two-compartment model to acknowledge this fact can be achieved easily. Because we do not have any evidence of model misspecification (fig. 4), the simple model accounts for the observed time course of carbon dioxide, which means that the information content of the data is not sufficient to estimate a higher number of parameters than used in a one-compartment model. Therefore, we favor the more parsimonious approach.

With regard to the interpretation of the results obtained, the following points should be made. First, as can be seen in figure 5, relatively high plasma concentrations of alfentanil can be tolerated during steady state conditions. The corresponding fractional alveolar ventilation of 0.72 (median) for a concentration of 250 μg/l clearly provides adequate oxygenation with an $F_{I_{O_2}}$ of 0.21 and atmospheric pressure at sea level (alveolar oxygen tension = approximately 82 mmHg, according to the alveolar gas equation[24]). However, the fractional alveolar ventilation of several persons at that concentration is closer to 0.5 (alveolar oxygen tension = approximately 66 mmHg), a clearly undesirable degree of respiratory depression. Furthermore, considering that similar concentrations were to be reached instantaneously, a precipitous decrease in the alveolar ventilation and, as a logical consequence, hypoxia, would certainly occur, as can be deduced from figure 6. Immediately after an

is depicted here. The plane referring to the population mean of the pharmacodynamic parameters has been shaded, and the individual measurements and the curve referring to steady state have been omitted.

alfentanil (opioid) bolus, high concentrations of the drug at a normal Pa_{CO_2} would lead to a pronounced decrease of alveolar ventilation. Thereafter, because carbon dioxide accumulation occurs and is a result of its respiratory stimulant effect, alveolar ventilation would increase again, even if the alfentanil (opioid) concentration had been kept constant. The arrows in the figure are intended to portray this situation.

Can we predict a safe alfentanil concentration for the spontaneously breathing patient? With the caveats of not taking into account anesthetic drug interactions and the stimulatory effect of pain on respiration,[31-33] a steady state concentration of 50 μg/l will decrease alveolar ventilation less than 23% from baseline in 97.5% of the patients. Steady state Pa_{CO_2} would be less than 53.6 mmHg in 97.5% of the patients. Regarding the fact that reported minimal effective concentrations for postoperative analgesia range from 15 μg/l to 60 μg/l,[34,35] this recommendation looks equally attractive when based on effectiveness data obtained in patients after surgery.

In conclusion, we developed a pharmacokinetic-pharmacodynamic model for the quantitative description of opioid-induced respiratory depression. As noted previously, several important questions must be considered regarding opioid-induced respiratory depression, and they could be answered quantitatively by applying the methods we described.

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