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·kg⁻¹·min⁻¹) was started while the patients were breathing oxygen-enriched air (fraction of inspired oxygen [FIO₂] = 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 (PₐCO₂) exceeded 55 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 (PₐCO₂). A mammillary two-compartment model was fitted to the pharmacokinetic data. The PₐCO₂ data were described by an indirect response model. The model accounted for the respiratory stimulation resulting from increasing PₐCO₂. 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 PₐCO₂. The following pharmacodynamic parameters were estimated (population means and interindividual variability): EC₅₀, 60.3 μg/l (32%); the elimination rate constant of carbon dioxide (Kₐ), 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 PₐCO₂ in maintaining alveolar ventilation in the presence of opioid.

Conclusions: The model described the data for the entire opioid–PₐCO₂ 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.)

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, 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.
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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\textsuperscript{13,14} accounts for the effect of opioids on the elimination of carbon dioxide rather than the $P_{\text{ac}}$ 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 ($P_{\text{co}_2}$) within the respiratory center, which can be approximated using the $P_{\text{ac}}$. 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 unmedicated 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 ($P_{\text{O}_2} = 0.5$) 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 ($P_{\text{e}CO_2}$) 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, $P_{\text{e}CO_2}$ 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.\textsuperscript{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 $P_{\text{ac}}$.

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 $P_{\text{ac}}$. We did this in response to several published reports regarding this issue.\textsuperscript{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 \(-20^\circ\text{C}\) 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.\textsuperscript{21} The recovery rate was 89%. The samples were analyzed by high-performance liquid chromatography (mobile phase: 0.05 M Na$_2$HPO$_4$, 55%; acetonitrile, 35%; isopropanol, 10%; column: Supelcosil DB-8 [250 \(\times\) 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 in-
teraction to reduce the influence of model misspecification
was used for all model fits, empirical Bayesian esti-

mation of the individual parameters, and simulations.22

The pharmacokinetic-dynamic analysis was per-
formed sequentially. The population means, the interin-
dividual variability, and the empirical Bayesian estimates
of the individual pharmacokinetic parameters were de-
termined first. Subsequently, the pharmacodynamic data
(Paco2) were analyzed with fixed individual pharmaco-
kine

tic parameters.

An exponential model was used to describe the inter-
dividual variability in the pharmacokinetic and the
pharmacodynamic parameters:

\[ \theta_{(n,i)} = \theta_{(n,m)} \cdot e^{\eta(i)} \]  

(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 \( \eta \) varies
randomly among individuals with a mean of zero and a
diagonal variance-covariance matrix \( \Omega^2 \).

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

\[ DV_{obs} = DV_{exp} \cdot (1 + \epsilon) \]  

(2)

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

Decisions between different models were made using
the Akaike information criterion.23 We checked for
model misspecification by plotting the ratio of the mea-
sured 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 tempera-
ture pressure dry conditions24), mass balance equations
can be used to describe volume changes. Constant tem-
perature, volumes, and pressures are directly propor-
tional; 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 \( P_{a_{CO_2}} \) normalized to atmospheric pressure in
our model.

\[ \frac{d}{dt} V_{a_{CO_2}} \cdot \frac{P_{a_{CO_2}}}{760} = k_{in}(t) - k_{out}(t) \]  

(3)

where \( V_{a_{CO_2}} \) is apparent volume of distribution of
carbon dioxide in the body (in l); \( P_{a_{CO_2}} \), 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 pres-
sure at sea level (in mmHg); \( k_{out}(t) \) is the product of the
(pulmonary) clearance (Cl; in l/min) and the \( P_{a_{CO_2}} \) at
time t divided by the barometric pressure.

\[ \frac{d}{dt} V_{a_{CO_2}} \cdot \frac{P_{a_{CO_2}}}{760} \]  

(4)

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

\[ \frac{d}{dt} V_{a_{CO_2}} \cdot \frac{P_{a_{CO_2}}}{760} \]  

(5)

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

\[ \frac{d}{dt} V_{a_{CO_2}} \cdot \frac{P_{a_{CO_2}}}{760} = 0 \]  

(6)

And therefore
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Under the assumption that carbon dioxide production remains constant, \( k_{\text{in}}(t) \) can be expressed as the product of the baseline value of the normalized \( \text{paco}_2 \) and alveolar ventilation.

\[
\frac{d}{dt} \text{V}_a \text{CO}_2 \cdot \frac{\text{paco}_2}{760} = \text{V}_{\text{alv}}(0) \cdot \frac{\text{paco}_2(0)}{760} - \text{V}_{\text{alv}}(t) \cdot \frac{\text{paco}_2(t)}{760}
\]

Rearranging for the change of \( \text{paco}_2 \), the dependent variable, over time yields

\[
\frac{d}{dt} \text{paco}_2 = \frac{\text{V}_{\text{alv}}(0) \cdot \text{paco}_2(0) - \text{V}_{\text{alv}}(t) \cdot \text{paco}_2(t)}{V_a \text{CO}_2}
\]

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, \( k_{\text{e}} \) (min\(^{-1}\)).

\[
\frac{d}{dt} \text{paco}_2 = k_e(0) \cdot \text{paco}_2(0) - k_e(t) \cdot \text{paco}_2(t)
\]

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 \( V_{\text{alv}} \). Opioids are known to reduce (alveolar) ventilation. Because the change in \( \text{paco}_2 \) 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 \( \text{paco}_2 \) using an indirect-response model. A linear model with a negative slope and a fractional \( E_{\text{max}}^\text{paco}_2 \) model were tested.

\[
V_{\text{alv}}(c, \text{paco}_2) = V_{\text{alv}}(0) \cdot \left( 1 - \frac{c(t)}{EC_{50} + c(t)} \right) \cdot \left( \frac{\text{paco}_2(t)}{\text{paco}_2(0)} \right)^{\frac{f}{1}}
\]

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

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

\[
\frac{d}{dt} \text{paco}_2 = \frac{\text{V}_{\text{alv}}(0) \cdot \text{paco}_2(0) - \text{V}_{\text{alv}}(t) \cdot \text{paco}_2(t)}{V_a \text{CO}_2} \cdot \left( 1 - \frac{c(t)}{EC_{50} + c(t)} \right) \cdot \left( \frac{\text{paco}_2(t)}{\text{paco}_2(0)} \right)^{\frac{f}{1}} \cdot \text{paco}_2(t)
\]

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 \( \text{paco}_2 \), corresponding to several alfentanil concentrations (50, 100, 150, 200, and 250 \( \mu \text{g/l} \)). Baseline alveolar ventilation was not measured, so
we cannot calculate absolute alveolar ventilation. However, because any change of $k_{al}$ must be attributed to a change in $V_{al}$, 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.

$$\frac{V_{al}(c_{ss}, P_{aCO_2}(c_{ss}))}{V_{al}(0)} = \left(1 - \frac{c_{ss}}{EC_{50} + c_{ss}}\right) \cdot \left(\frac{P_{aCO_2}(c_{ss})}{P_{aCO_2}(0)}\right)^F$$  

(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 $P_{aCO_2}$ 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 $\alpha_1$-antagonistic and $\alpha_2$-agonistic properties, to treat hypertension after 17 min. No 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.

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

<table>
<thead>
<tr>
<th>Estimated Parameters</th>
<th>Population Mean (% CV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volumes [l]</td>
<td></td>
</tr>
<tr>
<td>Central ($V_1$)</td>
<td>5.35 (26)</td>
</tr>
<tr>
<td>Peripheral ($V_2$)</td>
<td>10.4 (---)</td>
</tr>
<tr>
<td>Clearances [l/min]</td>
<td></td>
</tr>
<tr>
<td>Central ($Cl_1$)</td>
<td>0.35 (42)</td>
</tr>
<tr>
<td>Peripheral ($Cl_2$)</td>
<td>0.54 (53)</td>
</tr>
</tbody>
</table>

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 $\eta$ 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 $e^{-\mu}$, where 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.
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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 (\( \text{Pa}_\text{CO}_2 \)) 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 \( \text{Pa}_\text{CO}_2 \) concentrations. A counterclockwise hysteresis can be observed.

Both by inspection of the residuals and by the Akaike information criterion, the fractional \( F_{\text{max}} \) 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 \( F_{\text{max}} \) model. Because we could not simultaneously estimate \( F \) and \( E_{50} \), 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 \( \text{Pa}_\text{CO}_2 \) data are superimposed on the simulation. The data from persons who did not
Table 2. Pharmacodynamic Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Population Mean (% CV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(k_m) (min(^{-1}))</td>
<td>0.088 (44)</td>
</tr>
<tr>
<td>(EC_{50}) ((\mu)g/l)</td>
<td>60.3 (32)</td>
</tr>
<tr>
<td>(F) (%)</td>
<td>4.0 (28)</td>
</tr>
</tbody>
</table>

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 \(\eta\) 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 \(e^{\frac{\eta}{2}}\). 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 \(P_{aCO_2}\), 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, \(P_{aCO_2}\), 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 \(P_{aCO_2}\) 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 \textit{et al.}\(^2\) 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 \(P_{aCO_2}\) 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 \textit{a priori} as a primary end point. Minute ventilation is influenced by \(P_{aCO_2}\) 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 \(P_{aCO_2}\), or \(P_{iCO_2}\), 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 \textit{versus} slow infusion, would lead to different time courses of \(P_{aCO_2}\), which would not be accounted for in

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Fig. 4. Measured and predicted partial pressures of carbon dioxide in arterial blood (PaCO₂) 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 PaCO₂ in the study population during and after an alfentanil infusion of 5.78 mg (median cumulative dose) in 30 min. The population

Fig. 5. (Top) Predicted partial pressures of carbon dioxide in arterial blood (PaCO₂) 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 PaCO₂ (●) and the 16 and 84% quartiles (- - -) are also shown.

the model, the estimate of the EC₅₀ 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 PaCO₂ 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 PaCO₂ values are superimposed (●). The measured PaCO₂ values of patients in whom the infusion was prematurely discontinued are included up to the respective stopping times.
The steady state ventilation can was calculated as described in Methods. The subscript \( \text{ss} \) refers to steady state.

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 constant of the indirect response model and the baseline value of \( \text{PaCO}_2 \) without compromising patient safety has been adequately achieved. As stated in Materials and Methods, the relation between alfentanil concentration and \( \text{PaCO}_2 \) 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, 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 \( \text{PaCO}_2 \) from the current to the new steady state level after a change of alveolar ventilation, the \( k_{ec} \) 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 (\( k_e \)). Because the product of \( k_{ec} \) and the baseline value of \( \text{PaCO}_2 \) \( (\text{PaCO}_2(0)) \), yields the fastest possible increase of \( \text{PaCO}_2 \) 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).

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 \( \text{PaCO}_2 \) 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.

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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).
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Fig. 6. (Top) The relation among plasma alfentanil concentration, the partial pressure of carbon dioxide in arterial blood (Paco$_2$), 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 Paco$_2$ 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 Paco$_2$ 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 Paco$_2$, 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 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.

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alfentanil (opioid) bolus, high concentrations of the drug at a normal PaCO₂ 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, 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 PaCO₂ 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, 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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