Mechanism-based Pharmacokinetic–Pharmacodynamic Modeling of the Antinociceptive Effect of Buprenorphine in Healthy Volunteers

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Background: The objective of this investigation was to characterize the pharmacokinetic–pharmacodynamic relation of buprenorphine’s antinociceptive effect in healthy volunteers.

Methods: Data on the time course of the antinociceptive effect after intravenous administration of 0.05–0.6 mg/70 kg buprenorphine in healthy volunteers was analyzed in conjunction with plasma concentrations by nonlinear mixed-effects analysis.

Results: A three-compartment pharmacokinetic model best described the concentration time course. Four structurally different pharmacokinetic–pharmacodynamic models were evaluated for their appropriateness to describe the time course of buprenorphine’s antinociceptive effect: (1) E_max model with an effect compartment model, (2) “power” model with an effect compartment model, (3) receptor association–dissociation model with a linear transduction function, and (4) combined biophase equilibration/receptor association–dissociation model with a linear transduction function. The latter pharmacokinetic–pharmacodynamic model described the time course of effect best and was used to explain time dependencies in buprenorphine’s pharmacodynamics. The model converged, yielding precise estimation of the parameters characterizing hysteresis and the relation between relative receptor occupancy and antinociceptive effect. The rate constant describing biophase equilibration (k_eq) was 0.00447 min⁻¹ (95% confidence interval, 0.00399–0.00595 min⁻¹). The receptor dissociation rate constant (k_d) was 0.0785 min⁻¹ (95% confidence interval, 0.0532–0.122 min⁻¹), and k_on was 0.0631 ml · ng⁻¹ · min⁻¹ (95% confidence interval, 0.0390–0.0872 ml · ng⁻¹ · min⁻¹).

Conclusion: This is consistent with observations in rats, suggesting that the rate-limiting step in the onset and offset of the antinociceptive effect is biophase distribution rather than slow receptor association–dissociation. In the dose range studied, no saturation of receptor occupancy occurred explaining the lack of a ceiling effect for antinociception.

BUPRENORPHINE is a semisynthetic opiate derived from the morphine precursor thebaine which has been used in clinical practice since 1979.¹ In patients, buprenorphine is used for treatment of acute and chronic pain using various administration modes, such as intravenous, sublingual, and spinal–epidural administration. Several studies have shown that buprenorphine binds to the µ receptor, producing typical µ-receptor agonist effects such as analgesia, sedation, nausea, delayed gastric emptying, and respiratory depression. The first receptor binding studies conducted classified buprenorphine as a partial agonist at the µ-opioid receptor.²

In theory, partial agonists display low intrinsic efficacy at their target receptor relative to full agonists. However, the relation between the partial agonist nature of buprenorphine and its analgesic effect is not well established. For example, data from distinct animal studies support partial agonistic activity for buprenorphine-induced antinociception.³,⁴ However, at relatively high doses, evidence for an inverse U-shaped dose–response relation has been obtained. In the meantime, it has become clear that shape of dose–analogesic response relations is dependent on the applied pain model. For example, in animal models for chronic pain, buprenorphine is fully effective over a wide dose range.⁵ Moreover, in a recent mechanism-based pharmacokinetic–pharmacodynamic modeling study, a full antinociceptive effect of buprenorphine in rats was observed.⁶ In addition, several studies have demonstrated full analgesic efficacy for buprenorphine over a wide dose range in volunteers and patients.⁷–¹⁰

Another aspect of buprenorphine’s pharmacologic profile is the slow receptor association–dissociation kinetics at the µ receptor.³,¹¹ In humans, upon parenteral administration, the time to the onset of analgesia is 10–30 min, and the duration of analgesic effect is 6–8 h.¹² The slow onset of analgesic effect complicates optimal dose titration of buprenorphine, while the slow offset of effect offers a clear advantage relative to other opiates, such as morphine and fentanyl, because it makes buprenorphine suitable for less frequent daily dosing. Recently, we have developed a mechanistic pharmacokinetic–pharmacodynamic model allowing separate characterization of biophase equilibration and slow receptor association–dissociation kinetics as determinants of time dependencies in buprenorphine’s antinociceptive effect in rats.⁶ These investigations showed that contrary to common belief, the slow onset and offset of the antinociceptive effect is determined by slow biophase equilibration kinetics, rather than slow receptor association–dissociation kinetics. Furthermore,
buprenorphine was shown to act as a full agonist with regard to the antinociceptive effect in rats.

The specific objectives of this study were to characterize the pharmacokinetic–pharmacodynamic correlation of buprenorphine in humans. Specifically, the objectives were (1) to determine whether the same pharmacokinetic–pharmacodynamic model as previously proposed for rats applies to human situation, (2) to estimate the various rate constants that determine the time course of the antinociceptive effect (i.e., biophase equilibration vs receptor association–dissociation kinetics), and (3) to determine the in vivo concentration–effect relation for antinociception.

Materials and Methods

Subjects
Thirty-four volunteers (17 men, 17 women; aged 18–30 yr) were recruited to participate in the investigation after approval was obtained from the Human Ethics Committee (Leiden University Medical Center, Leiden, The Netherlands) and after giving written and oral informed consent. The subjects were healthy and did not have a history of illicit substance abuse. All women used oral contraceptives. The subjects were asked not to eat or drink for at least 6 h before the study. Each subject participated once in the study. After arrival in the research unit, an arterial line was placed in the left or right radial artery during local anesthesia (for blood sampling). In the contralateral arm, an intravascular line was inserted (for drug infusion).

Study Design
The study had a double-blind, randomized design. There were six treatment levels covering a wide dose range: (1) four subjects received 0.05 mg/70 kg intravenous buprenorphine, (2) four subjects received 0.1 mg/70 kg intravenous buprenorphine, (3) eight subjects received 0.2 mg/70 kg intravenous buprenorphine, (4) five subjects received 0.3 mg/70 kg intravenous buprenorphine, (5) eight subjects received 0.4 mg/kg intravenous buprenorphine, and (6) five subjects received 0.6 mg/70 kg intravenous buprenorphine. Eight individuals received placebo treatment. Buprenorphine or placebo was administered over a 30-s period. The local pharmacy performed randomization and prepared 10-ml syringes for buprenorphine before the experiment. Buprenorphine (Temgesic, 0.3 mg/ml) was obtained from Reckitt & Coleman Ltd. (London, United Kingdom) and was dissolved in 0.9% NaCl up to a volume of 5 ml.

The Acute Pain Model
Acute pain was induced by an electrical current through two surface electrodes (Red Dot; 3M, London, Ontario, Canada) placed on the skin overlaying the tibial bone (shin bone) of the left leg. The electrodes were attached to a computer interfaced current stimulator, which was locally designed and constructed. The intensity of the noxious stimulation was increased from 0 mA in steps of 0.5 mA per 1 s. The stimulus train consisted of a square-wave pulse of 0.2 ms duration applied at 10 Hz and had a cutoff at 128 mA. The subjects were instructed to press a button on a control panel when the stimulus became painful (pain threshold) and when no further increase in stimulus intensity was acceptable (pain tolerance). Upon pressing the pain tolerance button, the stimulus train ended. Because the subjects were naive to pain and analgesia experiments, they were trained before the study for approximately 1 h in which several stimulus trains were applied. These data were discarded. After a subsequent resting period, baseline pain variables were obtained. Pain assessment was performed three times before drug infusion and at fixed times after drug infusion. The current intensities at which pain threshold and tolerance occurred were automatically collected and stored on the hard disk of a computer for further analysis. In case blood sampling coincided with pain assessment, the pain testing preceded the sampling. Because pain tolerance is considered more reliable in detecting true opioid-induced analgesic effect, we performed the pharmacokinetic–pharmacodynamic analysis on the pain tolerance data.

Determination of Buprenorphine Concentrations
Blood samples (10 ml) for the determination of the buprenorphine concentration were collected using lithium heparin Vacutainers (Becton Dickinson, United Kingdom). After centrifugation, the resultant plasma was transferred into screw-cap polypropylene tubes and stored at less than –20°C in until analysis. For the determination of buprenorphine concentrations in plasma, a validated gas chromatography–mass spectrometry method was used. To plasma aliquots of 1.0 ml, 1.0 ml 0.5N NaOH, 25 ml internal standard stock solution (2H4-buprenorphine), and 7 ml toluene/diisopropylether (3:1 vol/vol) were added. After shaking the samples for 20 min and centrifugation, the organic phase was transferred to conical glass tubes and stored at approximately –20°C until derivatization. Samples were evaporated with a stream of nitrogen, and the residues were reconstituted in 50 ml of 1% derivatization reagent in toluene and 20 ml of 0.2% triethylamine in toluene. After 1 min reaction time at room temperature, the samples were washed with 300 ml water and 2 ml toluene. After the washing step, the organic phase was transferred to glass vials and evaporated to dryness under a weak stream of nitrogen. The residues were resolved in 25 ml toluene for measurement. Measurements were performed on a Finnigan MAT 4500 gas chromatography–mass spectrometry system (San Jose, CA). The mass spectrometer was operated in the negative ion chemical ionization.
mode with ammonia as reagent gas. Selected ion monitoring was performed for m/z 708 for buprenorphine and m/z 712 for internal standard. Human plasma used as control for interferences contained no peaks while analysis for buprenorphine was performed. Calibration curves were linear (r > 0.99) from 25.0 to 10,000 pg/ml, using weighted (1/x^2) linear regression. The lower limit of quantification was 25.0 pg/ml using 1 ml plasma. The overall accuracy and precision for calibration standards and quality controls analyzed during the study were well within 11% at all concentrations. All concentration data presented refer to buprenorphine free base.

Pharmacokinetic–Pharmacodynamic Modeling Procedure

The pharmacokinetic and pharmacodynamic parameters of buprenorphine were estimated using nonlinear mixed-effects modeling as implemented in the NONMEM software (version V, level 1.1; University of California, San Francisco, California; 1999).14 The population analysis approach, which takes into consideration both intranidividual and interindividual variability, was undertaken using the first-order conditional estimation method with η-e interaction (FOCE interaction). All fitting procedures were performed on an IBM (Armonk, NY)–compatible computer (Pentium IV, 1,500 MHz) running under Windows NT with the Microsoft FORTRAN Powerstation 4.0 compiler (Microsoft, Redmond, WA). An in-house available S+PLUS 6.0 (Insightful Corp., Seattle, WA) interface to NONMEM was used for data processing and management (including tools to perform predictive check and nonparametric bootstrap) and graphical data display.

Pharmacokinetic–Pharmacodynamic Model Development Strategy

The following method of approach for the development of the pharmacokinetic-pharmacodynamic model was used. In the first approximation, the structural part of the model was optimized on the data. In the next stage, interindividual variability was added to the model parameters, and statistical refinement of the random model was applied by means of covariance matrix analysis. In addition, the residual error model was determined. Finally, the relation between pharmacokinetic-pharmacodynamic model parameters and covariate terms was explored, and significant covariates were incorporated in the model.15,16 When possible, the physiologic relevance of the parameter–covariate relation was considered in the covariate selection. Individual post hoc pharmacokinetic parameter estimates served as input to the pharmacodynamic model. Model selection was based on model parameter estimates and the confidence intervals of the fixed and random parameters, parameter correlations, likelihood ratio test, and visual inspection of goodness-of-fit plots. Plots of individual observed versus population or individual predicted values and weighted residuals versus time or population predicted values were used to detect systemic deviations from the model fits.

Pharmacokinetic Data Analysis

To determine the basic structural pharmacokinetic model, the two- and three-compartment model with first-order elimination was tested. Using the likelihood ratio test, the significance level was set at α = 0.01, which corresponds to a reduction of 6.6 units in objective function value (OFV; chi-square distribution) to discriminate between two nested structural models after inclusion of one additional parameter. Based on model selection criteria, a three-compartment model with first-order elimination from the central compartment was selected to describe the time course of the buprenorphine concentration in plasma. The model was coded in the ADVAN11 TRANS4 subroutine and allowed the estimation of the parameters Cl, V1, V2, V3, Q2, and Q3. The random part of the model selected to describe interindividual variability in the pharmacokinetic parameters assumed a log-normal distribution of the model parameters over the population. Therefore, an exponential distribution model was used to account for interindividual variability:

$$P_i = P_{\text{tot}} \cdot \exp(\eta_i),$$

in which P_i is the individual value of model parameter P, P_{\text{tot}} is the typical value (population value) of parameter P in the population, and η_i is the normally distributed intersubject random variable with mean zero and variance $\sigma^2$. The coefficient of variation of the structural model parameters is expressed as percentage of the root mean square of the interindividual variance term. Selection of an appropriate residual error model was based on inspection of the goodness-of-fit plots. Interindividual variability was added on the model parameters by stepwise addition. A ΔOFV of 6.6 points was required to maintain interindividual variability on a structural model parameter. Afterward, the relative importance of each interindividual variability term was reassessed by deletion of each term one by one from the structural model parameters. An increase of more than 10.8 points (chi-square distribution, P < 0.001, df = 1) in OFV was regarded as significant for maintenance of interindividual variability on a model parameter. After establishment of the basic pharmacokinetic model, potential correlations between parameters were tested in a covariance matrix analysis in NONMEM (OMEGA BLOCK option). A drop of 6.6 points in OFV indicated the presence of a significant correlation between parameters. The statistical model used to quantify intranidividual variability in bu-
buprenorphine plasma concentration had the general form
\[ C_{\text{obs,ij}} = C_{\text{pred,ij}} \cdot (1 + e_{\text{ij}}), \] (2)
in which \( C_{\text{obs,ij}} \) is the \( j \)th observed concentration in the \( i \)th individual, \( C_{\text{pred,ij}} \) is the predicted concentration, and \( e_{\text{ij}} \) is the normally distributed residual random variable with mean zero and variance \( \sigma^2 \). The residual error term contains all the error terms that cannot be explained and refers to, for example, measurement and experimental error (e.g., error in recording sampling times) and structural model mis-specification.

**Mechanism-based**

**Pharmacokinetic–Pharmacodynamic Analysis**

Various structurally different pharmacokinetic–pharmacodynamic models were evaluated for their appropriateness to describe the time course of buprenorphine’s antinociceptive effect in healthy volunteers. To this end, pharmacokinetic–pharmacodynamic models were selected and tested on the basis of their ability to discriminate between distinct biologic processes causing time dependencies in the in vivo pharmacodynamics. To account for hysteresis between buprenorphine concentration in plasma and antinociceptive effect, the following pharmacokinetic–pharmacodynamic models were evaluated: (1) effect compartment model,\(^{17}\) (2) receptor association–dissociation model,\(^{18}\) (3) combined biophase equilibration/receptor association–dissociation model.\(^{6}\)

Another important question to be answered is whether ceiling effect for antinociception occurs in the studied dose range. To determine the shape of the function describing the relation between buprenorphine concentration and antinociceptive effect, the in vivo concentration–effect relations were characterized by an effect compartment model in combination with (1) the sigmoid \( E_{\text{max}} \) model and (2) the “power” model,\(^{19}\) which is of the form
\[ E = E_0 \cdot \left( 1 + 0.25 \cdot \left( \frac{C_e}{C_{25}} \right)^\gamma \right), \] (3)
where \( E \) is the antinociceptive effect, \( E_0 \) is the baseline response, \( C_{25} \) is the effect site concentration causing 25% increase in current for pain tolerance, and \( \gamma \) is a shape parameter.

In the final model, the time course of buprenorphine’s antinociceptive effect was analyzed using a dynamic receptor model with a linear transduction function. An important feature of this model is that it allows separation of biophase equilibration kinetics from receptor association–dissociation kinetics to account for time dependencies in the in vivo pharmacodynamics. This involves the estimation of the first- and second-order rate constants for receptor association and dissociation in combination with a single rate constant for biophase equilibration. Drug distribution to the site of action (biophase) was characterized on the basis of an effect compartment model.\(^{17}\) The rate of change of biophase drug concentrations can be described as follows:
\[ \frac{d[C_e]}{dt} = k_{\text{eo}} \cdot \left( [C_p] - [C_e] \right), \] (4)
where \( k_{\text{eo}} \) is a first-order distribution rate constant describing the rate of change of drug concentration in the effect compartment, \([C_p]\) represents the plasma concentration, and \([C_e]\) represents the effect site concentration. At the site of action, the drug can bind to the \( \mu \) receptor. Following the law of mass action, the rate of drug–receptor binding \((d[C_eR]/dt)\) is proportional to the drug concentration \([C_e]\) and the free receptor concentration \([R]\):
\[ \frac{d[C_eR]}{dt} = k_{\text{on}} \cdot [C_e] \cdot [R] - k_{\text{off}} \cdot [C_eR], \] (5)
where \( k_{\text{on}} \) is a second-order rate constant describing the rate of association and \( k_{\text{off}} \) is a first-order rate constant describing the rate of dissociation of the drug–receptor complex. Under the assumption that the concentration of drug is in excess compared with the free receptor concentration and that the total number of receptors \(([R_{\text{tot}}])\) is equal to the sum of drug-bound receptors \(([C_eR])\) and unbound receptors \(([R])\), equation 5 can be rearranged into
\[ \frac{d[C_eR]}{dt} = k_{\text{on}} \cdot [C_e] \cdot ([R_{\text{tot}}] - [C_eR]) - k_{\text{off}} \cdot [C_eR]. \] (6)
The total amount of receptors \(([R_{\text{tot}}])\) could not be measured in vivo and therefore was set to unity. Consequently, an apparent relative estimate of in vivo fractional receptor binding is obtained. The apparent fractional receptor binding was directly related to the antinociceptive effect according to the following equation:
\[ E = \frac{E_0}{1 - [C_eR]}, \] (7)
where \( E \) is the antinociceptive effect and \( E_0 \) is the baseline antinociceptive response. The steady state solution of equations 6 and 7 is equal to the “power” model presented in equation 3.

**Pharmacokinetic and Pharmacokinetic-Pharmacodynamic Model Validation**

The predictive performance and precision of the population pharmacokinetic model was evaluated by model validation.\(^{20}\) Internal validation was conducted by means of a nonparametric bootstrap technique. Briefly, 1,000 bootstrap replicates were generated by sampling randomly
from the original data set with replacement. Subsequently, the data sets were fitted one at a time to the final population pharmacokinetic model. The mean, SE, coefficient of variation, and lower and upper 95% prediction intervals of the model parameter values were calculated and compared with the typical model parameter values from the original study. Because of long run times of the population pharmacokinetic–pharmacodynamic model in NONMEM, no bootstrap validation was performed.

**Sensitivity Analysis**

To determine the reliability and robustness of an alternative modeling outcome to changes in the pharmacodynamic parameter $k_{eo}$, we have conducted a sensitivity analysis. The parameter $k_{eo}$ was fixed to values ±50% in 10% increments, and the objective function values were evaluated and mapped over the range of fixed $k_{eo}$ values selected.

**Results**

**Pharmacokinetics**

A three-compartment model with first-order elimination from the central compartment was used to describe the time course of buprenorphine concentration in plasma. The observed buprenorphine concentration-versus-time profiles stratified to dose are displayed in figure 1. The concentration-time profiles of typical individuals, predicted by the population pharmacokinetic parameter estimates of $Cl$, $V_1$, $V_2$, $V_3$, $Q_2$, and $Q_3$ are shown as solid lines in the respective figures. The population pharmacokinetic estimates of the final model are presented in table 1.

All parameters, including the random model parameters, were estimated precisely with an acceptable coefficient of variation (3.5–36.3%). Interindividual variability was low for the parameters $Cl$ and $V_3$ (17.3% and 22.9%, respectively) and relatively high for $V_1$, $V_2$, and $Q_2$ (58.6–93.4%). Residual variability was taken into account using a proportional error model and resulted in a prediction error of 14.5% over the total studied concentration range. Several covariate relations were explored by visual inspection of the covariate versus Bayesian pharmacokinetic parameters estimates and by performance of generalized additive modeling analysis. However, in NONMEM, no significant improvement of the model fit was detected after inclusion of the covariates in the structural pharmacokinetic model.

![Fig. 1. Individual buprenorphine concentration–time profiles for the different treatment groups (0.05–0.6 mg/70 kg). The observed concentrations (closed circles) and population predictions (thick line) are depicted.](http://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=/data/journals/jasa/931074/)
Finally, the predictability and stability of the population pharmacokinetic model was evaluated by model validation. The precision and stability of the developed population pharmacokinetic model was explored using internal validation. The final population model estimates for $Cl$, $V_1$, $V_2$, $V_3$, $Q_2$, and $Q_3$ and their respective 95% confidence intervals were supported by the results of the bootstrap validation (table 1). The estimates of the interindividual variability of the pharmacokinetic parameters were almost identical to those obtained with the bootstrap validation. The fits of the 1,049 bootstrap replicates demonstrated the stability and robustness of the developed population pharmacokinetic model.

**Mechanism-based Pharmacokinetic–Pharmacodynamic Modeling**

Baseline values of pain tolerance (± SEM) were $18.9 ± 2.8$ and $17.9 ± 2.6$ mA in men and women, respectively. After bolus intravenous administration of buprenorphine, the currents needed for pain tolerance significantly increased relative to baseline in both sexes. The maximal peak effect was reached after approximately 70–100 min. To demonstrate the appropriateness of the various pharmacokinetic–pharmacodynamic models to characterize the time course of antinociceptive effect in humans, model discrimination was performed. The likelihood ratio test was used to evaluate the performance of (1) the sigmoid $E_{max}$ model with effect compartment model, (2) the “power” or “Leiden” model (equation 7) with effect compartment model, (3) the receptor association–dissociation model, and (4) the combined biophase equilibration/receptor association–dissociation model including a linear function to describe the relation between apparent fractional receptor occupancy and antinociceptive effect. The minimum values of the objective function for the pharmacokinetic–pharmacodynamic models 1, 2, 3, and 4 were 3407.2, 3406.4, 3458.3, and 3354.3, respectively.

The minimum values of the objective function for the various pharmacokinetic–pharmacodynamic models show that the combined biophase equilibration/receptor binding model described the time course of antinociceptive effect best, yielding estimates for $k_{on}$, $k_{off}$, and $K_D$. The pharmacodynamic parameter estimates are presented in table 2. The placebo antinociceptive response is shown in figure 2. Figure 3 shows the time course of antinociceptive effect for all individuals stratified to the different treatment groups. The antinociceptive responses in typical individuals, predicted on the basis of

![Fig. 2. Influence of placebo treatment on the time course of the antinociceptive effect.](image-url)

Table 1. Parameter Estimates of the Final Population Pharmacokinetic Model for Buprenorphine and the Stability of the Parameters Using the Bootstrap Resampling Procedure

<table>
<thead>
<tr>
<th>Parameter Estimate</th>
<th>Original Data Set</th>
<th>1,049 Bootstrap Replicates</th>
</tr>
</thead>
<tbody>
<tr>
<td>$Cl$, l/min</td>
<td>1.45 ± 0.035</td>
<td>1.43 ± 0.040</td>
</tr>
<tr>
<td>$V_1$, l</td>
<td>8.39 ± 0.149</td>
<td>8.03 ± 0.240</td>
</tr>
<tr>
<td>$V_2$, l</td>
<td>23.3 ± 0.207</td>
<td>23.0 ± 0.309</td>
</tr>
<tr>
<td>$V_3$, l</td>
<td>127 ± 0.59</td>
<td>125 ± 0.67</td>
</tr>
<tr>
<td>$Q_2$, l/min</td>
<td>155 ± 0.123</td>
<td>1.51 ± 0.165</td>
</tr>
<tr>
<td>$Q_3$, l/min</td>
<td>0.953 ± 0.063</td>
<td>0.948 ± 0.71</td>
</tr>
</tbody>
</table>

Interindividual variability

- $\omega_{Cl}$, %: 17.3 ± 2.27
- $\omega_{V_1}$, %: 70.8 ± 2.10
- $\omega_{V_2}$, %: 93.4 ± 2.05
- $\omega_{V_3}$, %: 22.9 ± 3.63
- $\omega_{Q_2}$, %: 58.6 ± 19.6

Residual variability

- Proportional error, %: 14.5 ± 18.8

CV = coefficient of variation.

Table 2. Population Pharmacodynamic Estimates and Interindividual Variability of the Combined Biophase Equilibration/Receptor Association–Dissociation Pharmacokinetic–Pharmacodynamic Model of Buprenorphine

<table>
<thead>
<tr>
<th>Parameter Estimate</th>
<th>CV of Parameter Estimate, %</th>
<th>Interindividual Variability,* %</th>
<th>CV of Variability Estimate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>$k_{on}$, ml·ng·min⁻¹</td>
<td>0.0631</td>
<td>19.5</td>
<td>—</td>
</tr>
<tr>
<td>$k_{off}$, min⁻¹</td>
<td>0.0785</td>
<td>28.2</td>
<td>115</td>
</tr>
<tr>
<td>$K_D$, ng/ml</td>
<td>1.244</td>
<td>—</td>
<td>28.0</td>
</tr>
<tr>
<td>$k_{ass}$, ml·min⁻¹</td>
<td>0.00447</td>
<td>16.9</td>
<td>44</td>
</tr>
<tr>
<td>$E_0$, mA</td>
<td>16.5</td>
<td>8.9</td>
<td>50</td>
</tr>
<tr>
<td>$\sigma^2$, mA²</td>
<td>13.6</td>
<td>34.0</td>
<td>—</td>
</tr>
</tbody>
</table>

For the fixed and random parameter estimates, the coefficient of variation (CV) is displayed.

* Exponential distribution model. † Not estimable. ‡ Secondary parameter ($K_D = k_{off}/k_{on}$). § $\sigma^2$ = additive residual error.
the population pharmacodynamic parameter estimates, are depicted as solid lines. All parameters were estimated precisely, with an acceptable coefficient of variation (< 50%). In figure 4, examples of nine individual fits of the antinociceptive effect are given, including the worst, median, and best fits determined on the basis of coefficient of variation ($R^2$) for three dose groups of buprenorphine (0.3 mg/70 kg, 0.4 mg/70 kg, and 0.6 mg/70 kg). Figure 5 shows the steady state receptor binding-antinociceptive effect relation for buprenorphine.

The population estimates characterizing receptor association-dissociation kinetics were estimated at $0.0631 \pm 0.0390$ (95% confidence interval, 0.0390–0.0872) ml · ng$^{-1}$ · min$^{-1}$ and 0.0785 (95% confidence interval, 0.0352–0.122) min$^{-1}$ for the parameters $k_{on}$ and $k_{off}$, respectively. The rate constant describing biophase equilibration kinetics, $k_{eo}$, was estimated at 0.00447 (95% confidence interval, 0.00299–0.00595) min$^{-1}$, which corresponds to $t_{1/2,keo} = 155$ min versus $t_{1/2,koff} = 8.8$ min. The equilibration dissociation constant $K_D$ was calculated from the ratio $k_{off}/k_{on}$ and was 1.24 ng/ml, which corresponds to 2.66 nM.

A sensitivity analysis was performed to assess the impact of changes in the pharmacodynamic parameter $k_{eo}$ on the predictive performance of the combined biophase equilibration/receptor association-dissociation model. The results of the sensitivity analysis are presented in figure 6 and show that the combined biophase equilibration/receptor association-dissociation model is sensitive to changes in the pharmacodynamic parameter $k_{eo}$.

No significant sex dependency was observed for the rate constants for receptor association-dissociation and biophase equilibration. This was tested by inclusion of the covariate sex on the structural pharmacodynamic parameters $k_{eo}$, $k_{on}$, and $k_{off}$ one at a time ($\Delta$OFV < 1). In addition, pretreatment pain tolerance values were not significantly different for males and females ($\Delta$OFV < 1).

Discussion

Recently, a mechanism-based pharmacokinetic-pharmacodynamic model was proposed to characterize and

![Fig. 3. Changes in pain tolerance in time after intravenous administration of buprenorphine. For each treatment group (0.05–0.6 mg/70 kg), the observed (closed circles) and mean population predicted (solid line) time courses of antinociceptive effect are shown.](http://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=/data/journals/jasa/931074/)
predict the time course antinociceptive effect of buprenorphine in rats. The model was used to predict buprenorphine brain concentrations, binding of buprenorphine to the \( \mu \)-opioid receptor in the brain, and ultimately the antinociceptive effect. To this end, the pharmacokinetic–pharmacodynamic model incorporated the term \( k_{\text{eo}} \) to describe biophase equilibration kinetics, the parameters \( k_{\text{on}} \) and \( k_{\text{off}} \) to characterize the receptor association–dissociation kinetics of buprenorphine at the \( \mu \)-opioid receptor, and a linear transduction function to describe the relation between relative receptor occupancy and antinociceptive effect.

The current investigation focuses on the pharmacokinetic–pharmacodynamic correlation of buprenorphine in humans. This is important because between species, both qualitative and quantitative differences may exist between biologic systems. In the current investigation, a number of structurally different pharmacokinetic–pharmacodynamic models were evaluated for their usefulness to describe the time course of the antinociceptive effect after administration of buprenorphine. Four different model were tested: (1) the sigmoid \( E_{\text{max}} \) model with effect compartment model, (2) the power or Leiden model (equation 3) with effect compartment model, (3) the receptor association–dissociation model, and (4) the combined biophase equilibration/receptor association–dissociation model. The combined biophase equilibration–antinociceptive effect relation for buprenorphine for all individuals. This relation is derived from equation 7. The closed circles represent all individual receptor binding versus predicted pain tolerance pairs.
tion/receptor association-dissociation model showed a significantly improved fit compared with an effect compartment model and the receptor association-dissociation model. Analysis of the data on the basis of the sigmoid $E_{\text{max}}$ model with effect compartment to the buprenorphine concentration-antinociceptive effect data showed that $E_{\text{max}}$ could not be estimated accurately and precisely (data not shown), indicating that despite the wide dose range tested, the maximum antinociceptive response has not been reached in these investigations. Furthermore, analysis of the data with the sigmoid $E_{\text{max}}$ with effect compartment model showed no improvement of the model fit compared with the power model, confirming that maximum antinociceptive effect has indeed not been achieved in the studied dose range. Because no estimate of $E_{\text{max}}$ could be obtained, it was postulated that in the studied dose range, no receptor saturation occurred.

This has important implications for the selection of the transducer function in the receptor association-dissociation model or the combined biophase equilibration/receptor association-dissociation model. Specifically, the transducer function describes the relation between receptor occupancy and the antinociceptive effect. In theory, the transducer function can take any shape. The selection of a transducer function is dependent on the pharmacologic behavior, reflected by partial or full agonistic activity, of a drug in the biologic system. On the basis of the observed lack of a maximum antinociceptive effect in the current study and the fact that buprenorphine behaves as a partial agonist in receptor assays, it is plausible to assume a linear transducer function to characterize the apparent receptor binding-effect relation. Upon administration of 0.6 mg/70 kg buprenorphine, a predicted maximum of 70% of the receptors is occupied (fig. 5). Moreover, in the studied dose range, the observed buprenorphine concentrations in plasma and predicted concentrations in the biophase are mainly below the estimated $K_D$ value. Much higher concentrations exceeding the $K_D$ (1.24 ng/ml) are required to achieve maximal receptor binding. Therefore, higher doses are needed to saturate receptor binding (100% receptor occupancy) and to obtain the maximum antinociceptive effect.

On the basis of the combined pharmacokinetic-pharmacodynamic model, it was shown that with values of the half-life of biophase equilibration ($t_{1/2,\text{keo}}$) and the receptor dissociation values ($t_{1/2,\text{koff}}$) of 155 min and 8.8 min, respectively, the rate of onset and offset of antinociceptive effect is predominantly determined by distribution of buprenorphine to the effect site. Interestingly, the estimated half-life time of biophase equilibration (155 min) in the current study is in the same range as has been reported for buprenorphine-induced analgesia (171 min). The influence of the pharmacodynamic parameter $k_{\text{eo}}$ on the time course of the antinociceptive effect was examined by sensitivity analysis based on the combined biophase equilibration/receptor association-dissociation model (fig. 6). The results of the sensitivity analysis showed that the pharmacokinetic-pharmacodynamic modeling outcome is influenced by biophase equilibration, indicating that $k_{\text{eo}}$ can be estimated reliably with the current experimental design. This underlines the importance of the application of the combined biophase equilibration/receptor association-dissociation model to characterize the time course of buprenorphine’s antinociceptive effect.

Distribution to the biophase constitutes a biologically plausible representation of the rate-limiting step in onset and offset of buprenorphine antinociceptive effect. Specifically, buprenorphine is a lipophilic opiate and is, similar to fentanyl, assumed to cross the blood-brain barrier readily. For these drugs, the delay in antinociceptive effect is most likely caused by drug distribution within the brain tissue. The elimination of buprenorphine from the brain is likely to be slow relative to the pharmacokinetics of buprenorphine in plasma, indicating that the elimination of buprenorphine from the brain is the rate-limiting step in terminating the drug’s action (fig. 7). This is in agreement with results from dedicated drug disposition studies that also show slow elimination of buprenorphine from the brain. Specifically, Pontani et al. reported that after administration of 0.2 mg/kg buprenorphine in rats, the decline of the buprenorphine concentration in the brain was markedly slower than from plasma ($t_{1/2,\text{brain}}$ 2.3 h vs. $t_{1/2,\text{plasma}}$ 1.4 h). In addition, using $^{[1]}$C]-buprenorphine as a positron emission tomography tracer to characterize buprenorphine disposition characteristics in the brain, it was also shown in

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**Fig. 7.** Time course of buprenorphine concentration in plasma (dashed line) and biophase (solid line) in a typical healthy volunteer after intravenous bolus administration of 0.4 mg/70 kg buprenorphine. The dotted line represents the apparent in vivo fractional receptor occupancy of buprenorphine. The elimination of buprenorphine from brain is slower than from plasma. The thick dashed–dotted line represents the $K_D$ value of 1.24 ng/ml. Note that most observed buprenorphine concentrations are below the estimated $K_D$ value.

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baboons that the elimination of buprenorphine from brain is slower than from plasma.

The onset and offset of the antinociceptive effect, which both determine the observed hysteresis in the time course of the antinociceptive effect, are influenced by different pharmacologic mechanisms. This is illustrated in figure 8, where the changes in the time to reach peak effect (T<sub>max</sub>) with k<sub>on</sub> (keeping K<sub>D</sub> or k<sub>off</sub>/k<sub>on</sub> constant) and k<sub>off</sub> is depicted. The value of the rate constant k<sub>off</sub> influences the observed time delay in the antinociceptive effect more than the rate constant for biophase equilibration (fig. 8A). This is in accordance with the observation that transport across the blood–brain barrier is much faster than binding of buprenorphine to the µ-opioid receptor (receptor association kinetics). On the other hand, biophase equilibration determines the buprenorphine disposition characteristics at the effect site and influences the biologic effect intensity and the duration of the antinociceptive effect (fig. 8B).

In mechanism-based pharmacokinetic–pharmacodynamic modeling, typically a distinction is made between drug-specific properties and biologic system specific properties. Drug specific properties comprise receptor affinity and intrinsic efficacy. In principle, drug specific properties can be predicted on the basis of information from in vitro bioassays. An important question is to what extent the rate constants for receptor association (k<sub>on</sub>) and dissociation (k<sub>off</sub>) could be predicted on the basis of in vitro bioassays. Drug-specific characteristics for buprenorphine, like receptor association–dissociation kinetics, have also been investigated in vitro. The results from these studies indicate the presence of high-affinity and low-affinity binding sites for buprenorphine in the spinal cord and a low-affinity binding site in the brain. In these in vitro experiments, the dissociation of buprenorphine from the µ-opioid receptor was characterized by an initial rapid phase (t<sub>1/2_koff</sub> = 5.6 min) followed by a slower phase (t<sub>1/2_koff</sub> = 166.4 min). The estimated in vitro dissociation half-life for buprenorphine of 8.8 min is in accordance with the reported in vitro value for the initial rapid phase of the dissociation of buprenorphine from the µ-opioid receptor.

Interestingly, receptor binding characteristics of buprenorphine have also been investigated in vivo using opioid receptor imaging with [11C]-buprenorphine as a positron emission tomography tracer in baboons. The dissociation rate constant for buprenorphine was reported to be 0.069 min<sup>-1</sup>, which is equivalent to a t<sub>1/2_koff</sub> of 10 min, which is again in close agreement with our results. These observations confirm the validity of the pharmacokinetic–pharmacodynamic model and indicate that the rate constants for receptor association and dissociation may be readily predicted from in vitro bioassays. Similar pharmacologic characteristics of the in vivo kinetics of onset and offset of buprenorphine’s antinociceptive effect were observed in rat. In rats, the drug-specific rate constants for receptor association and dissociation were estimated at 0.0228 ml · ng<sup>-1</sup> · min<sup>-1</sup> and 0.0731 min<sup>-1</sup>, respectively. Therefore, in rats and humans, the kinetics of receptor association and dissociation of buprenorphine are in the same range, indicating that the µ-opioid receptor functions in a nearly identical manner in both species. On the other hand, the rate constant for biophase equilibration is different between rat (k<sub>eo</sub> = 0.0242 min<sup>-1</sup>) and human (k<sub>eo</sub> = 0.00447 min<sup>-1</sup>). In contrast to receptor association–dissociation drug characteristics, the rate constant for biophase equilibration is dependent on the biologic system and may therefore vary among species (e.g., differences in brain distribution characteristics). An intriguing question is whether, taking into consideration allometric scaling laws, biophase equilibration kinetics could be predicted in humans on the basis of the estimated rate constant for biophase equilibration from preclinical studies. This will be subject of further investigations in our laboratory.

An important issue is the potency and intrinsic activity of buprenorphine for its antinociceptive effect relative to other opiates like morphine. Using a pharmacokinetic–pharmacodynamic model, the concentration–analytic effect relation of morphine has also been characterized. On this basis, morphine’s potency for acute pain was estimated to be in the range of 32.9–76.5 nm. The buprenorphine-versus-morphine potency ratio indicate that buprenorphine is 12–29 times more potent than morphine for µ-opioid receptor-induced antinociception. This is in agreement with the general perception...
that buprenorphine is 20–40 times more potent than morphine.8,38,59

In conclusion, a recently proposed mechanism-based pharmacokinetic–pharmacodynamic model had been successfully applied to characterize the time course of antinociceptive effect of buprenorphine in healthy volunteers. The model was able to separate biophase equilibration and receptor association– dissociation properties. Pharmacokinetic–pharmacodynamic analysis suggests that time dependencies in the pharmacodynamics of buprenorphine with respect to antinociception were mainly determined by biophase equilibration kinetics. Similar characteristics for the time course of the antinociceptive effect have been reported for rats. This suggests that this mechanism-based approach constitutes a realistic reflektion of the kinetics of buprenorphine action in vivo. Pharmacokinetic–pharmacodynamic analysis of the in vivo concentration–effect relation showed no ceiling effect for the antinociceptive effect of buprenorphine.

In the current analysis, maximum predicted receptor occupancy was 70% in the studied dose range. Higher doses are necessary to saturate receptor binding and to achieve a maximum antinociceptive effect.

References