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## Chapter 4

# Stochastic Pharmacokinetic-Pharmacodynamic Analysis of the Effect of Transdermal Buprenorphine on Electroencephalogram and Analgesia\*

OPIOIDS ARE USED WIDELY in the treatment of moderate-to-severe cancer and noncancer pain.<sup>91</sup> There are currently 2 monumental challenges in the treatment of chronic pain: the objective assessment of opioid effect in a setting in which abuse and accidental overdose is highly prevalent and the need for proper dosing strategies. The efficacy of opioids and other centrally acting analgesics often is determined rather subjectively by the use of quantitative sensory testing, questionnaires, and so on.<sup>59</sup> To determine a suitable objective biomarker as a measure of opioid drug effect is challenging.

One possibility is the electroencephalography (EEG), which is a widely available and noninvasive tool for recording brainwave activity simultaneously from multiple brain regions. Several drug classes that act on the central nervous system generate a reproducible effect on the EEG obtained at rest.<sup>46,50</sup> For example, Liley *et al.*<sup>48</sup> showed that the effect of remifentanyl on frontally recorded resting EEG could be dissociated from the EEG effects of propofol, an anesthetic acting at a different receptor target in the central nervous system. The EEG is therefore of great interest in evaluating the effect of drugs used in anesthesia and pain treatment.

Because opioid effects are delayed relative to their plasma concentration profile, because of the time needed to reach and interact with the opioid receptors, a pharmacokinetic-pharmacodynamic (PK-PD) analysis may be used.<sup>49,52</sup> PK-PD analysis links dose to effect and makes it possible to take inter- and intraindividual variability into consideration when designing appropriate dosing strategies.<sup>52</sup> Indeed, a drug-induced EEG effect can produce a dynamic outcome applicable in PK-PD modeling, which may be

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\* A E Olesen, E Olofsen, T Andresen, C Graversen, A M Drewes, A Dahan, *Anesth Analg* 2015; 121:1165-1175

used to determine population-predicted values for dose and effect, leading to a more rational approach for effective dosing regimens.

In the current study, we assessed the effect of transdermal buprenorphine on the resting EEG and experimental pain in healthy volunteers to elucidate the PK-PD profile of transdermal buprenorphine. Transdermal buprenorphine is an appealing treatment for chronic pain, because it is an agonist for analgesia but a partial agonist for respiratory depression over its clinical dose range.<sup>26,25</sup> Modeling the effect of an opioid given by a transdermal patch should consider the possibility that the absorption rate may not be constant. For example, changes in skin temperature may lead to changes in drug absorption from the patch.<sup>56</sup> Hence, the PK-PD model that we apply should take into account a variable uptake of drug from patch or dermal reservoir.

Here, we applied a stochastic PK-PD technique that accounts for varying drug absorption as first described by Tornøe *et al.*<sup>89</sup> We previously applied a stochastic PK-PD (SPKPD) model to assess the effect of ketamine on cardiac output and chronic pain relief.<sup>64,24</sup>

We measured 2 opioid effects: pain relief and changes in EEG. Rather than using conventional indices derived from the EEG, such as spectral edge, median frequency, peak frequency, or power spectrum, we used the ratio of slow-to-fast EEG frequencies as a biomarker for opioid effect. Dichotomizing the frequency spectrum into low- and high-frequency components has the advantage in that it compensates for interindividual variability in the frequency distributions and minimizes the number of EEG features traditionally obtained from the various frequency bands.<sup>88</sup>

We hypothesize (1) that the resting EEG is a reliable and objective surrogate for buprenorphine's effect and (2) that SPKPD analysis allows the computation of the time-dependent variability in drug absorption from patch to blood. Our approach will lead to a better understanding of the behavior of the patch.

## 4.1 Methods

This double-blind, randomized, placebo-controlled, crossover study was approved by the North Denmark Region Committee on Health Research Ethics and the Danish Health and Medicines Authority and registered at ClinicalTrials.gov under number NCT00647127. The study was performed according to the principles of Good Clinical Practice of the European Union from June 2008 until August 2009 in the research laboratories of Mech-Sense, Aalborg University Hospital, Denmark, and all subjects gave written informed consent. Descriptions and analyses of portion of the data were reported previously.<sup>6,5,7,33,81,82</sup> These reports include data on the effect of buprenorphine and fentanyl on evoked potentials, analgesia, and antihyperalgesia using a set of nociceptive tests (including pressure pain, ultraviolet B light burn injury, intradermal capsaicin-induced hyperalgesia, and conditioned pain modulation).

### 4.1.1 Study Design

Twenty-two healthy, opioid-naive male volunteers (mean age  $23.1 \pm 3.8$  years) were recruited to participate in the study. Subjects received a transdermal patch (Norspan<sup>TM</sup> 144-h; Norpharma, Vedbæk, Denmark) or a placebo patch (Norpharma) identical in appearance for 144 hours, followed, after removal of the patch, by a 3-day follow-up period.

A washout period of 10 days was observed between treatments. The subjects were hospitalized during the treatment phase, with regular assessments of blood pressure, heart rate, respiratory rate, and oxygen saturation.

An independent pharmacist performed the randomization using an electronic randomization list downloaded from randomization.com. Sample size calculation was based on previous studies on the influence of opioids on experimental heat pain and was used to set the number of subjects to detect an effect in these previous descriptive studies.<sup>81,82</sup> To show an increase in pain tolerance threshold of 2°C (with a power of 90%, SD = 1.70 and  $\alpha = 0.05$ ), 16 subjects are required in each group. Taken into account the variability and possible loss of data, the number in each group was increased to 22.

### **Blood Sampling and Buprenorphine Assay**

Nine microliters of venous blood samples were collected in EDTA blood collection tubes at baseline and 6, 9, 12, 24, 36, 48, 60, 72, 78, 84, 96, 120, 144, 168, 192, and 216 hours after application of the patches. The blood samples were immediately centrifuged at 4°C at 3000 rpm for 15 minutes. Next, plasma was separated into two 2-mL polypropylene tubes (the second sample served as duplicate). Both tubes were stored at -80°C until analysis. The buprenorphine analysis has been published before.<sup>6</sup>

### **Thermal Cutaneous Stimulation**

The response to a noxious thermal stimulus was obtained at baseline and 24, 48, 72, and 144 hours after application of the patches. Pain was applied using a thermode (TSA II NeuroSensory Analyser; Medoc Ltd, Ramat Yishai, Israel) applied to the right volar forearm. The temperature increased from a baseline of 32°C to a maximum of 52°C with a rate of 1°C/s. The subject pressed a button on reaching the heat pain tolerance threshold. Three consecutive stimulations were performed, and the average was computed. All subjects were familiarized with the procedure before the study.

### **The Electroencephalogram**

The resting EEG was recorded at baseline and 4, 24, 48, 72, and 144 hours after application of the patches. An EEG amplifier (NuAmp; Neuroscan, El Paso, TX) was used to record the electrical activity on the scalp. Two electrodes were placed at Cz and CPz locations according to the international 10-20 system. In addition, one electrode was mounted at the right earlobe serving as reference, whereas one electrode was placed 2 cm frontal to the Cz electrode serving as ground electrode. The electrodes were mounted using electrode gel to reduce the impedance to < 5 k $\Omega$ , and the positions of the electrodes were maintained during the experiment by using an elastic fixation cap (Carefix Head, Ikast, Denmark). The EEG data were recorded with a sampling rate of 1 kHz. The data were recorded with an online notch filter at 50 Hz and band pass filter with cutoff frequencies of 0.5 and 300 Hz. Resting EEG recordings were obtained after pain tests and blood sampling by a research nurse in a quiet room with dimmed light as participants lay in supine position with eyes open.

The EEG signals were processed off-line. The processing included the following steps: (1) Artifact rejection by visual inspection, leaving at least 1 minute of valid recording for further analysis (Neuroscan version 4.3.1; Compumedics, El Paso, TX); and (2) high-pass

filtering to remove DC offset and linear detrending by a first-order Butterworth filter with cutoff frequency 0.5 Hz performed in MATLAB (The MathWorks Inc., Natick, MA).

## 4.1.2 Data Analysis

### EEG Analysis: Time-Frequency Analysis

Time-frequency analysis can be applied in several ways; recent studies showed that a continuous wavelet transform (CWT) is advantageous over more traditional methods such as the Fourier transform.<sup>3</sup> The CWT is based on a mother wavelet function, which was a complex Morlet wavelet for the current study.<sup>70,84,35,27</sup> The time-frequency coefficients of the Cz EEG channel were rectified and integrated over time to obtain the marginal distribution in the frequency bands:  $\delta$  (0.5-3.5 Hz),  $\theta$  (3.5-7.5 Hz),  $\alpha_1$  (7.5-10.5 Hz),  $\alpha_2$  (10.5-13.5 Hz),  $\beta_1$  (13.5-18.5 Hz),  $\beta_2$  (18.5-24.5 Hz), and  $\beta_3$  (24.5-32 Hz). The frequency bands were normalized into percentage of the total power (0.5-32 Hz). An EEG ratio was used to evaluate the results. The EEG ratio was defined as the percentage sum of the slow conducting frequency bands ( $\delta + \theta + \alpha_1$ ) divided by the percentage sum of the fast conducting frequency bands ( $\alpha_2 + \beta_1 + \beta_2 + \beta_3$ ).

### Stochastic Model for Buprenorphine Absorption

We assume that the absorption rate of buprenorphine from patch into the disposition compartment varied over time; see Figure 4.1. The noise in the absorption (*i.e.*, process noise) was modeled using the following stochastic differential equations:<sup>89,64,24,90,61,53,42</sup>

$$dA_a(t)/dt = -k_a(t) \cdot A_a(t) \quad (4.1)$$

$$dA_d(t)/dt = k_a(t) \cdot A_a(t) - k_e(t) \cdot A_d(t) \quad (4.2)$$

$$k_a(t) = \exp(Z(t)) \quad (4.3)$$

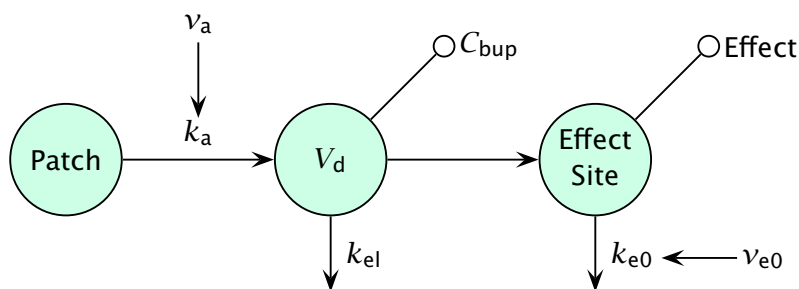
$$dZ(t) = \sigma_w \cdot dw(t), \quad (4.4)$$

where  $A_a(t)$  is amount of drug in the absorption compartment at time  $t$  ( $A_a(0) = 20$  mg),  $A_d(t)$  is the amount of drug in the disposition compartment,  $k_a(t)$  is the absorption rate (set to zero when the patch is removed),  $k_e(t)$  is the elimination rate constant,  $Z$  is a link variable,  $w(t)$  is the Wiener process, and  $\sigma_w$  is the standard deviation of changes in  $Z(t)$  per the square root of time (*i.e.*,  $\sigma_w$  is the variability in the absorption rate constant in the log domain). A Wiener process is a model of Brownian random motion resulting from a sum of many small normally distributed fluctuations.<sup>32</sup> This parameterization constrains  $k_a(t)$  to be positive;  $k_a(t = 0)$  is a variable to be estimated. The buprenorphine concentration is given by the ratio of  $A_d$  and the volume of distribution,  $V_d$ .

### Pharmacodynamic (PD) Analysis

The PD part of the models assumes an effect compartment in which the drug appears with a delay:

$$dC_e(t)/dt = k_{e0} \cdot (C_d(t) - C_e(t)) \quad (4.5)$$



**Figure 4.1:** Schematic representation of the stochastic pharmacokinetic-pharmacodynamic model, in which the pharmacokinetic part consists of the transfer of drug from patch to disposition compartment  $V_d$  with rate constant  $k_a$ . Fluctuations in  $k_a$  are modeled by noise process  $v_a$ .  $V_d$  is linked to the effect-site compartment.  $k_{e0}$  is the blood-effect-site equilibration constant; possible fluctuations are modeled by noise process  $v_{e0}$ .

where  $C_d(t)$  is the drug concentration in the disposition compartment at time  $t$ ,  $C_e(t)$  is the effect-site concentration at time  $t$ , and  $k_{e0}$  is the blood-effect-site equilibration rate constant. The PD effect (EF) was assumed to be related to  $C_e(t)$ :

$$EF(t) = BLN \cdot (1 + (C_e(t)/C_{100})^y) \quad (4.6)$$

where BLN is the baseline value,  $C_{100}$  is the effect-site concentration causing a 100% increase in surrogate effect measure, and  $y$  is a shape parameter. Finally, an additional stochastic differential equation for  $k_{e0}$  was tested.

## Statistical Analysis

The population pharmacokinetic-pharmacokinetic (PK-PD) analyses were performed by implementing the models in the statistical software package NONMEM (version VII, level 2; Icon Development Solutions, Hanover, MD). For the SPKPD analysis, an extended Kalman filter was incorporated.<sup>90,61,53,42</sup> NONMEM's subroutine ADVAN13 was used to integrate drug amounts in absorption, disposition, and effect compartments and additional Kalman filter state variables. PK and PD data were analyzed simultaneously. The 2 PD data sets were analyzed separately (PK/resting EEG, PK/skin pain tolerance). Residual error was assumed to have both an additive and a relative error for concentrations and only an additive error term for the PD end points. Goodness-of-fit plots were created for the PK and PD data to check for model adequacy and possible outliers. P values  $< 0.01$  were considered significant.

## 4.2 Results

### 4.2.1 EEG Spectrum and Pain Response

EEG data were not available from 3 subjects because of technical problems with the EEG equipment. These subjects did provide pain data. The mean age of the subjects ( $\pm$  SD,  $n = 22$ ) was  $22.5 \pm 1.8$  years, mean height  $181.2 \pm 5.8$  cm, and mean weight  $73.3 \pm 7.4$  kg.

Figure 4.2 displays the impact of buprenorphine and placebo on the spectral distribution of the EEG at baseline and after 72 hours of patch application.

Figure 4.2E shows a greater shift from fast to slow activity of the EEG spectrum in the buprenorphine group after 72 hours (dotted and solid red lines) than in the baseline group (dotted and solid blue lines). The absolute and relative individual and average EEG ratio and pain tolerance data are given in Figures 4.3 and 4.4. Compared with placebo, buprenorphine increased EEG ratio by 0.2 to 0.3 points (paired t test:  $P = 0.006$  at  $t = 48$  hours;  $P = 0.0006$  at 72 hours;  $P = 0.001$  at 144 hours) and heat pain tolerance threshold by 1 to 2°C (paired t test:  $P = 0.0008$  at 48 hours;  $P = 0.005$  at 72 hours;  $P = 0.03$  at 144 hours).

## 4.2.2 PK-PD Analysis

The individual and average plasma buprenorphine concentrations are given in Figure 4.3E and Figure 4.3F. A separate PK-PD analysis was performed on the PK/resting EEG ratio data and the PK/skin pain tolerance data. In none of the analyses, parameter  $\gamma$  was significantly different from 1, indicating that the PD effect was linearly related to the buprenorphine effect-site concentration.

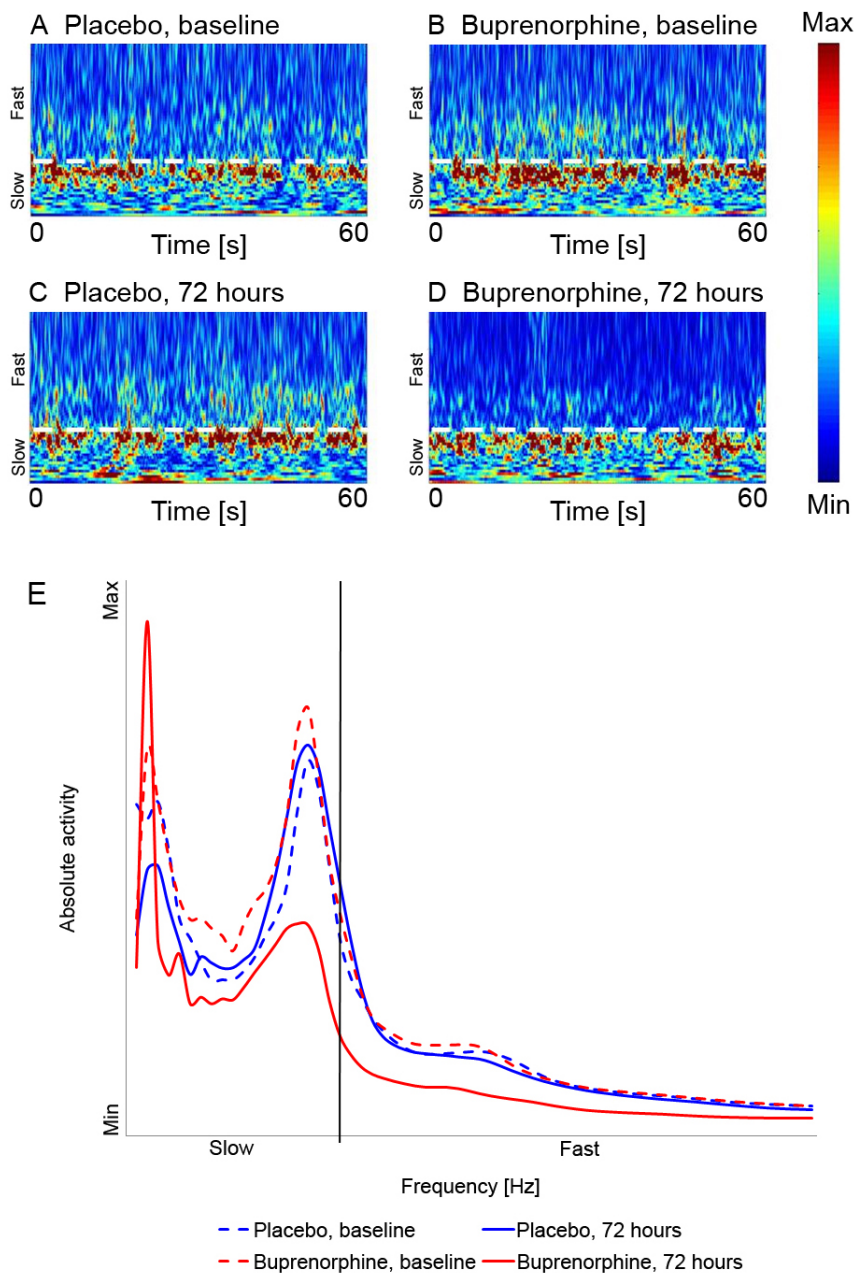
### PK Analysis

The PK parameters are given in Table 4.1. The initial value for the absorption rate constant ( $k_a$ ) was  $0.005 \text{ h}^{-1}$ , elimination rate constant  $0.04 \text{ h}^{-1}$ , and volume of distribution 11 L. Similarly, the standard deviation of the noise of the absorption process and standard deviations and residual errors were of similar magnitude between analyses ( $\sigma_w$  0.11  $1/\sqrt{h}$ ,  $\sigma_1$  0.01 ng/mL, and  $\sigma_2$  0.14). The variability in the absorption rate is quantified by  $\sigma_w$ , indicating that  $k_a$  varies by 0.11 per hour and, for example, will range between approximately  $0.003 \text{ h}^{-1}$  and  $0.008 \text{ h}^{-1}$  after 10 hours of the patch application if no information via PK or PD samples is obtained.

PK goodness-of-fit plots are given in Figure 4.5, and examples of PK data fits are given in Figure 4.6, (panels G, H, and I). Both show that the SPKPD model adequately described the PK data. For none of the PK parameters was interindividual error estimable, which indicates that the variability in the parameter estimates was mainly caused by within-subject, rather than between-subject, variability. In none of the subjects did drug absorption remain constant during the 144-hour buprenorphine treatment, as observed by the fluctuations in  $k_a$  over time (Figure 4.6, panels J, K, and L).

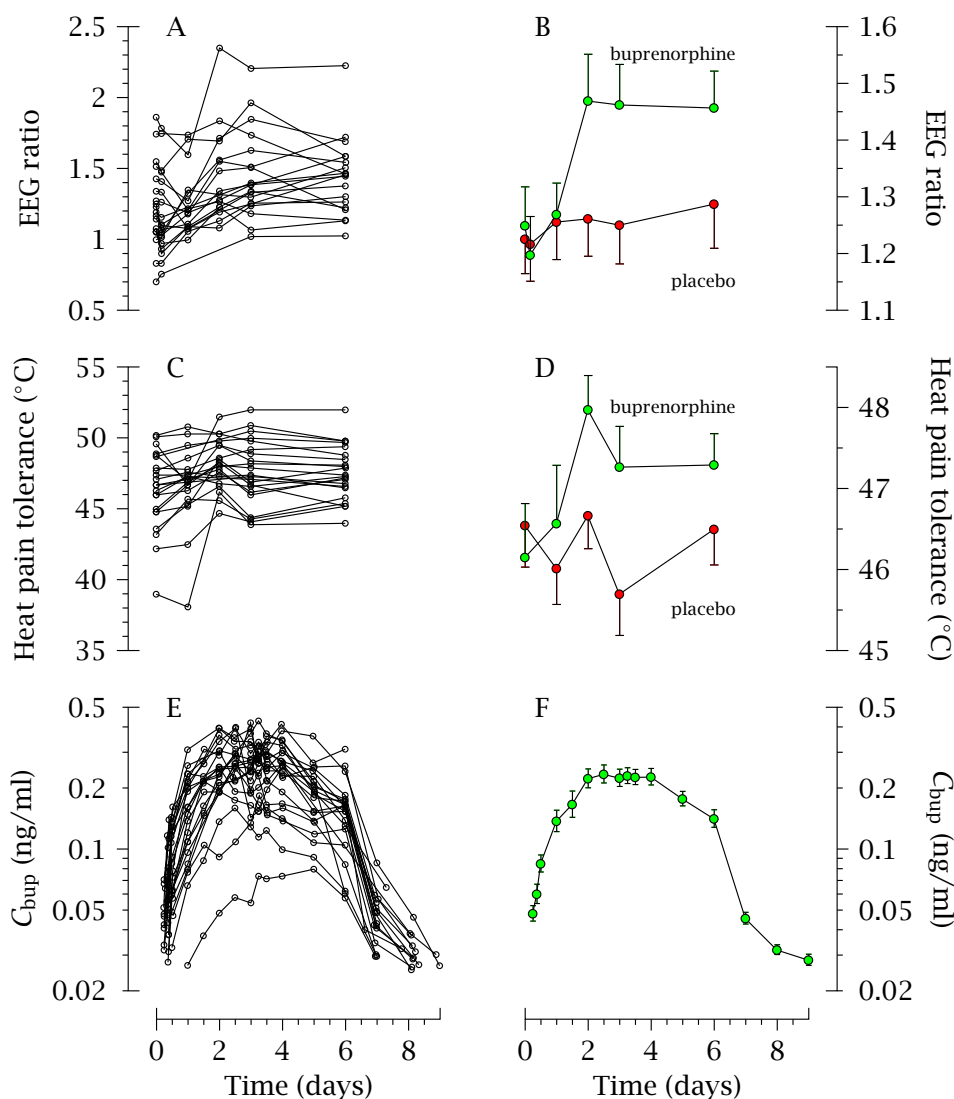
### PD Analysis

Examples of PD data fits are given in Figure 4.6 (panels A-C and D-F). For EEG ratio, the best, median, and worst fits are given as based on the coefficient of determination ( $R^2$ ). Note that a negative value for  $R^2$  was observed for the worst fit, indicating that the fit is worse than just using the mean of the data. PD parameter estimates are given in Table 4.1. For all data fits, the 95% confidence intervals were calculated (broken lines in Figure 4.6). These intervals are based on both the measurement and the prediction errors and may therefore vary in time, depending on the information obtained from the measurements (PK or PD), which is fed back to the stochastic differential equations of

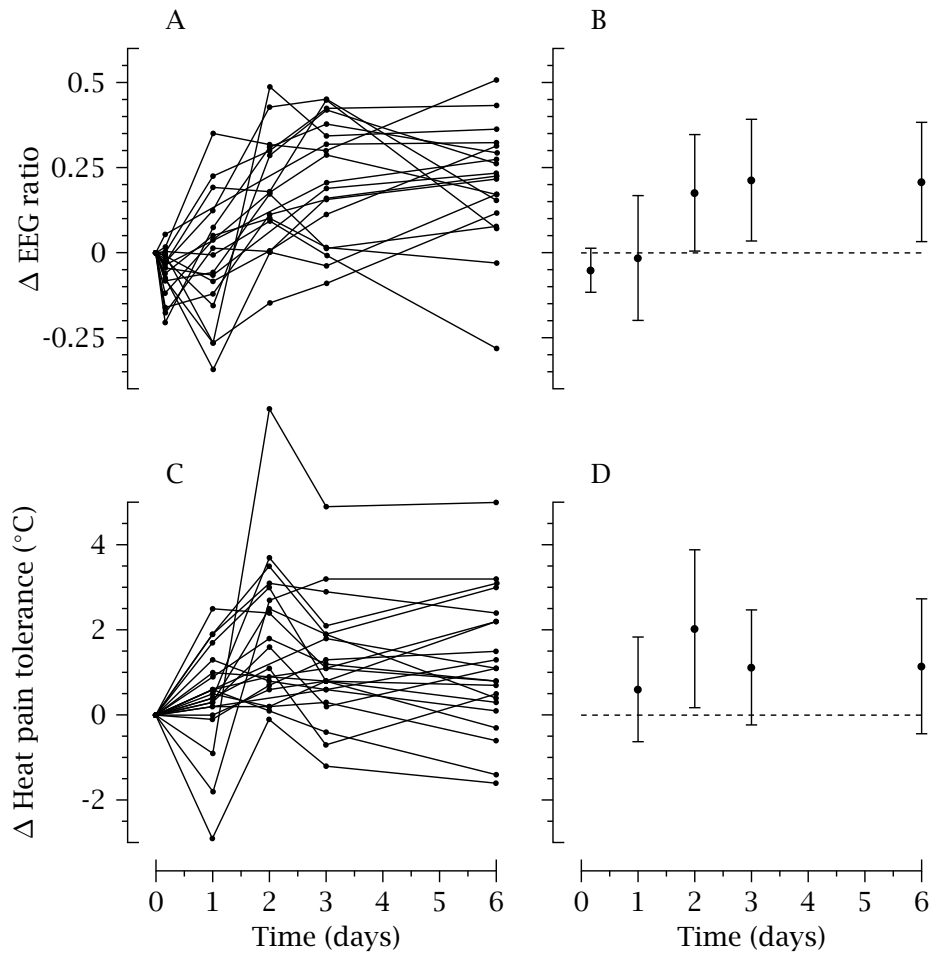


**Figure 4.2:** A-E: Examples from one subject of the spectral distribution of the resting electroencephalography measurement at baseline (A and B) and after 72 hours of placebo (C) and buprenorphine (D). A shift is visible after 72 h of buprenorphine treatment from fast toward slow oscillations. E: Frequency *versus* absolute activity for buprenorphine and placebo treatment at baseline and 72 h. Absolute activity was calculated by a continuous wavelet transform using a complex Morlet function with bandwidth parameter of 128 Hz and wavelet center frequency of 0.5 Hz.

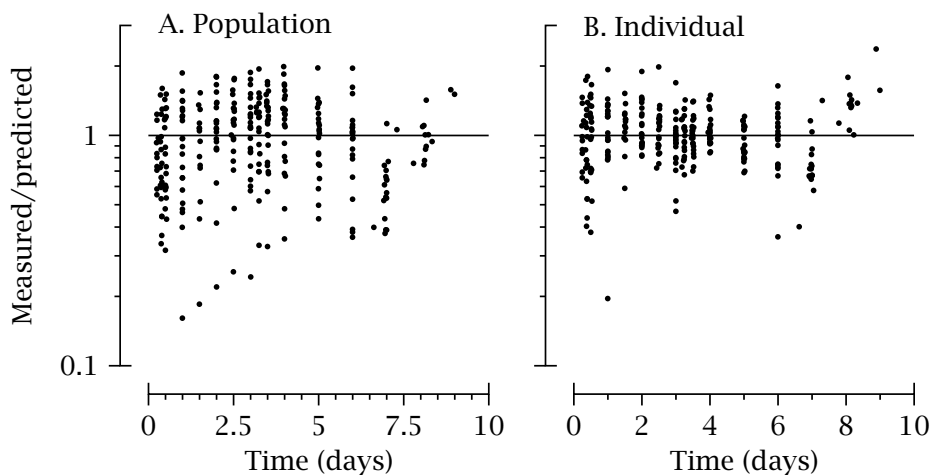




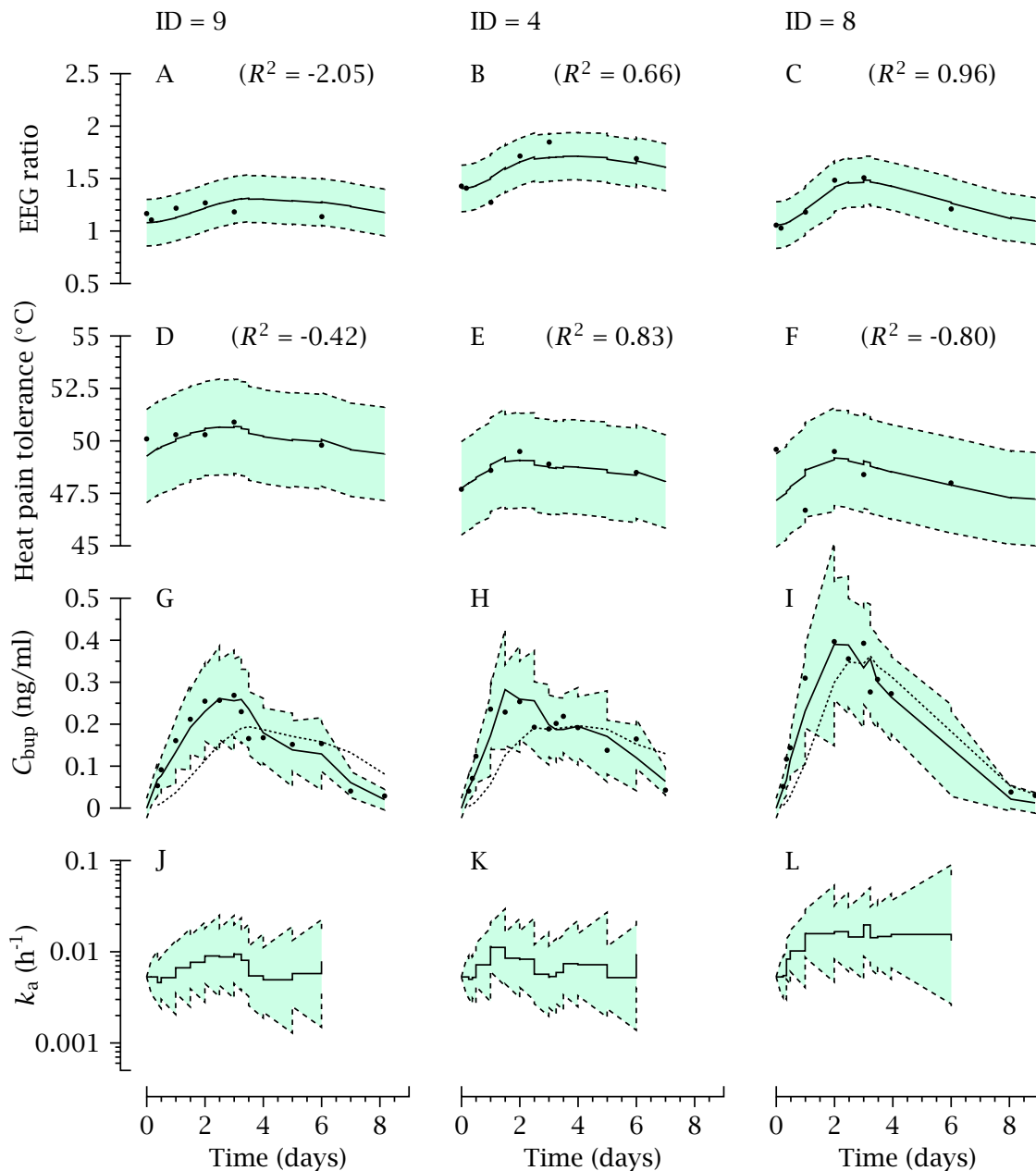
**Figure 4.3:** Individual data (A) and averages (B) of the effect of a 144 h (6 day) administration of buprenorphine by transdermal patch on the electroencephalography (EEG) ratio. In panel B, the placebo averages are given. Over time buprenorphine increased the EEG ratio significantly compared with placebo. Individual data (C) and averages (D) of the effect of the 144 h buprenorphine patch on skin heat pain tolerance (units °C). In panel D, the placebo averages are included. Over time buprenorphine increased skin heat pain tolerance significantly compared with placebo. Individual (E) and average (F) buprenorphine plasma concentrations during and 2.5 days after the buprenorphine patch application. In panels A, C, and E, each line represents one subject; in panels B, D, and F, the data are mean  $\pm$  SEM.



**Figure 4.4:** A-D: Individual and average electroencephalography ratio and pain tolerance relative to baseline values.



**Figure 4.5:** Pharmacokinetic goodness-of-fit plots. **A:** Measured *versus* population-predicted plasma buprenorphine concentrations. **B:** Measured *versus* individual predicted plasma buprenorphine concentrations.



**Figure 4.6:** Best (A), median (B), and (C) worst data fits of the electroencephalography (EEG) ratio and corresponding data fits of skin heat pain tolerance (D, E, and F), and plasma buprenorphine concentration (G, H, and I). Goodness of fit was based on the coefficient of determination ( $R^2$ ). The bottom graphs (J, K, and L) depict the changing absorption rate constant ( $k_a$ ) over time. The black dots are the measured data; the continuous lines are the data fit; and the broken lines are the 95% confidence intervals; in panels G-I, the dotted lines are the buprenorphine effect-site concentrations (derived from EEG data). Note that at  $t = 144$  h the patch was removed ( $k_a$  set to 0).

**Table 4.1:** Parameter Estimates of the SPKPD Analysis

Parameter	Resting EEG ratio		Heat pain tolerance	
	Estimate $\pm$ SEE	$\omega^2 \pm$ SEE	Estimate $\pm$ SEE	$\omega^2 \pm$ SEE
$k_a$ ( $\text{h}^{-1}$ )	$0.005 \pm 0.001$	<i>a</i>	$0.005 \pm 0.001$	<i>a</i>
$k_e$ ( $\text{h}^{-1}$ )	$0.04 \pm 0.002$	<i>a</i>	$0.04 \pm 0.002$	<i>a</i>
$V_d$ (L) <sup>b</sup>	$11.6 \pm 0.9$	<i>a</i>	$11.4 \pm 0.9$	<i>a</i>
$\sigma_w$ ( $1/\sqrt{h}$ )	$0.11 \pm 0.01$	<i>a</i>	$0.11 \pm 0.01$	<i>a</i>
$\sigma_1$ (ng/mL)	$0.01 \pm 0.003$		$0.01 \pm 0.003$	
$\sigma_2$	$0.14 \pm 0.03$		$0.14 \pm 0.03$	
BLN <sup>c</sup>	$1.18 \pm 0.06$	$0.03 \pm 0.03$	$46.5 \pm 0.60$	$0.02 \pm 0.006$
$t_{1/2, k_{e0}}$ (h)	$24.8 \pm 8$	$0.7 \pm 0.4$		
$C_{100}$ (ng/mL)	$0.90 \pm 0.10$	<i>a</i>	$9.2 \pm 2.5$	<i>a</i>
$\sigma_3$	$0.11 \pm 0.01$		$1.10 \pm 0.20$	

SPKPD = stochastic pharmacodynamic-pharmacodynamics;

EEG = electroencephalography; SEE = standard error of estimate;

$\omega^2$  = between-subject variability (in the log-domain);

$k_a$  = initial absorption rate constant, *i.e.*, at  $t = 0$ ;

$k_e$  = elimination rate constant;  $V_d$  = volume of distribution;

$\sigma_w$  = standard deviation of the noise process ( $Z$  in Equations (4.3) and (4.4));

$\sigma_1$  and  $\sigma_2$  = standard deviations of additive and relative error;

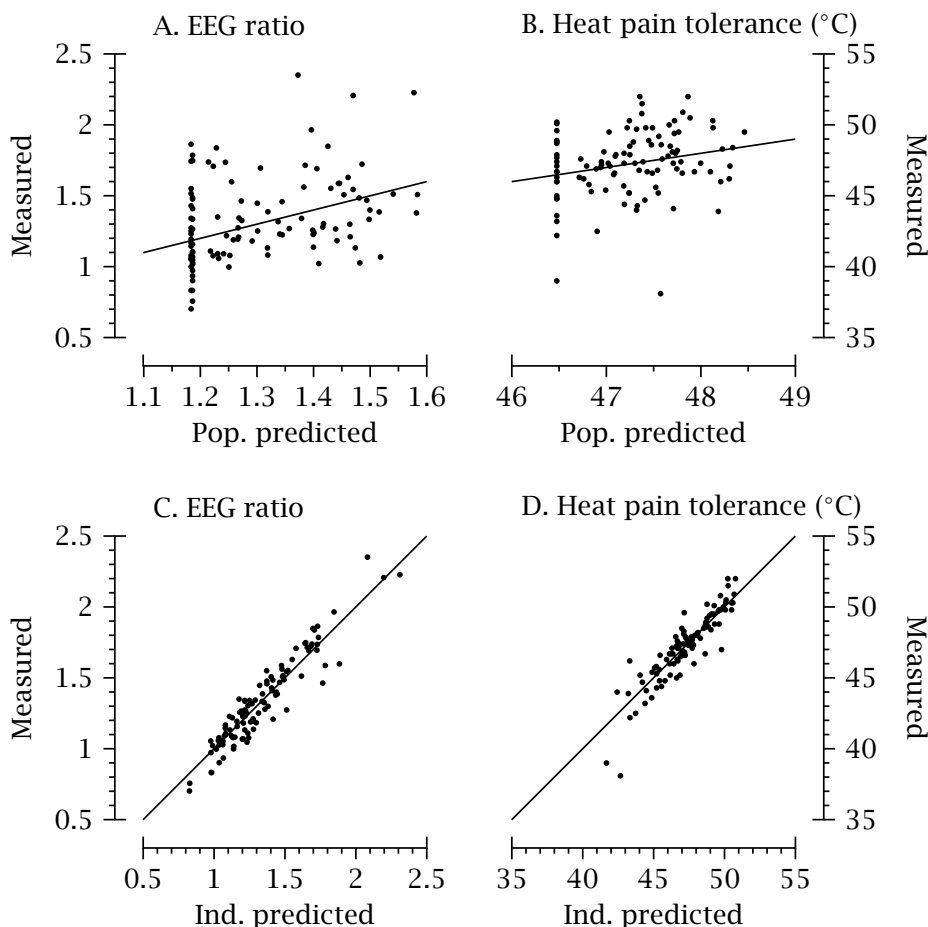
respectively, for the concentration estimates;

BLN = baseline value;  $t_{1/2, k_{e0}}$  = blood-effect-site equilibration half-life;

$C_{100}$  = effect-site concentration causing a 100% increase (*i.e.*, doubling) in effect;

$\sigma_3$  = additive error for the effect estimates with unit for pain tolerance  $^{\circ}\text{C}$ ;

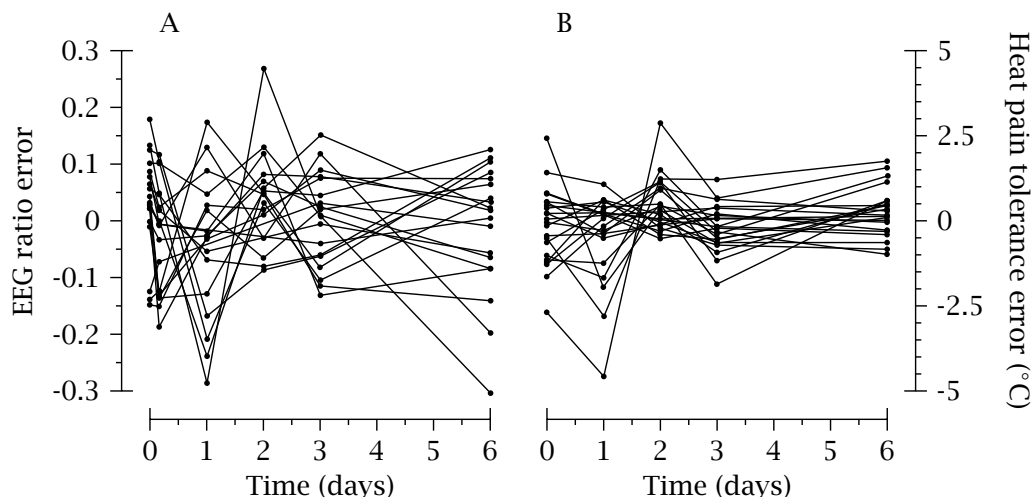
<sup>a</sup>Not estimable; <sup>b</sup> $V_d$  values are relative to the buprenorphine bioavailability (it is assumed that 100% of the buprenorphine absorbed from the patch becomes systemically available); <sup>c</sup>Unit for BLN pain tolerance is  $^{\circ}\text{C}$ .



**Figure 4.7:** Pharmacodynamic goodness-of-fit plots. **A** and **C**, Measured electroencephalography (EEG) ratio *versus* individual-predicted and population-predicted EEG ratio. **B** and **D**, Measured skin heat pain tolerance (units °C) *versus* individual-predicted and population-predicted skin heat pain tolerance.

the model.<sup>90</sup> The updated states of the differential equations can be seen as sudden updates of the estimated absorption rates, concentrations, and PD end points.

Goodness-of-fit plots are given in Figures 4.7 to 4.9. Figure 4.7 shows the measured *versus* population-predicted (Fig. 4.7A, EEG ratio; and Fig. 4.7B, heat pain tolerance) and measured *versus* individual-predicted (Fig. 4.7C, EEG ratio; and Fig. 4.7D, heat pain tolerance) data. Figure 4.8 shows the spaghetti plots for EEG ratio error (Fig. 4.8A) and heat pain tolerance error (Fig. 4.8B). Figure 4.9 gives the log-likelihood profiles of the (PK and PD) model parameters. The objective function is most sensitive to changes in parameter BLN (EEG ratio, Fig. 4.9E; and heat pain tolerance, Fig. 4.9F) and least sensitive to changes in  $t_{1/2, k_{e0}}$  (half-life from  $k_{e0}$ ) (EEG ratio, Fig. 4.9C). A bootstrap analysis (1000 simulations drawing random samples from the subject pool) was performed to assess the sensitivity of the model output to exclude subjects from the data set (data not shown). The results show that excluding subjects did not result in systematic changes in parameter values. Overall, the inspection of the data fits and diagnostic plots indicates that the SPKPD adequately described the data.



**Figure 4.8:** Spaghetti plots for electroencephalography ratio (A) and pain tolerance (B) showing residual error *versus* time.

### Hysteresis

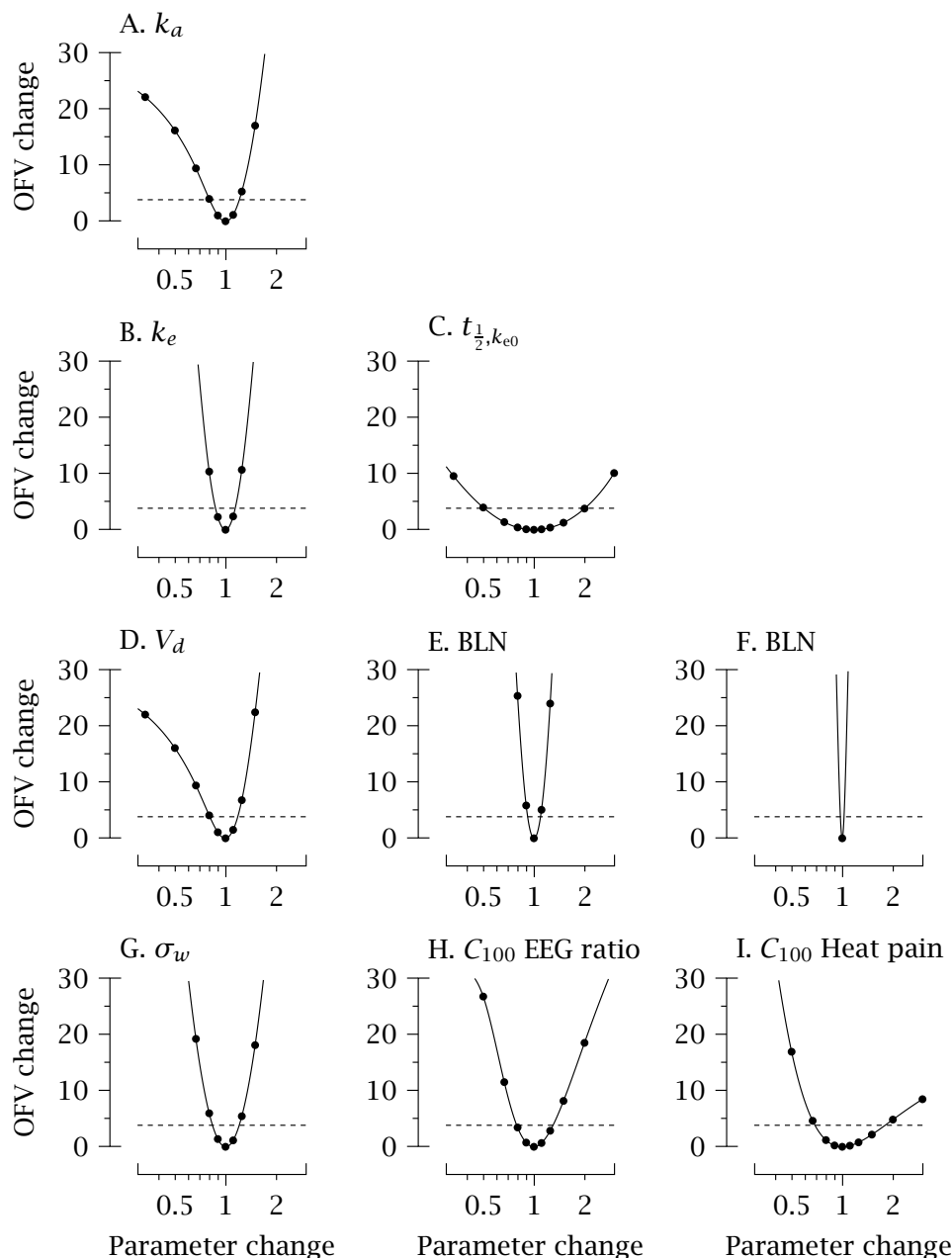
In Figure 4.10, examples of buprenorphine plasma concentration *versus* effect are plotted and show that no significant hysteresis was detected for pain tolerance. In contrast, a significant hysteresis was observed for EEG ratio, with a value for parameter  $t_{1/2, k_{e0}}$  of  $24 \pm 8$  hours. The log-likelihood profile of parameter  $t_{1/2, k_{e0}}$  shows a rather flat surface profile with values that range from -50% to +100% of the optimal estimate within its 95% confidence interval (Fig. 4.9C). Removal of parameter  $t_{1/2, k_{e0}}$  from the model resulted in an increase of Objective Function Value  $> 20$  points. A stochastic differential equation to account for fluctuations of  $k_{e0}$  did not improve the data fits. Hence, this approach was discarded.

### EEG Ratio *versus* Heat Pain Tolerance

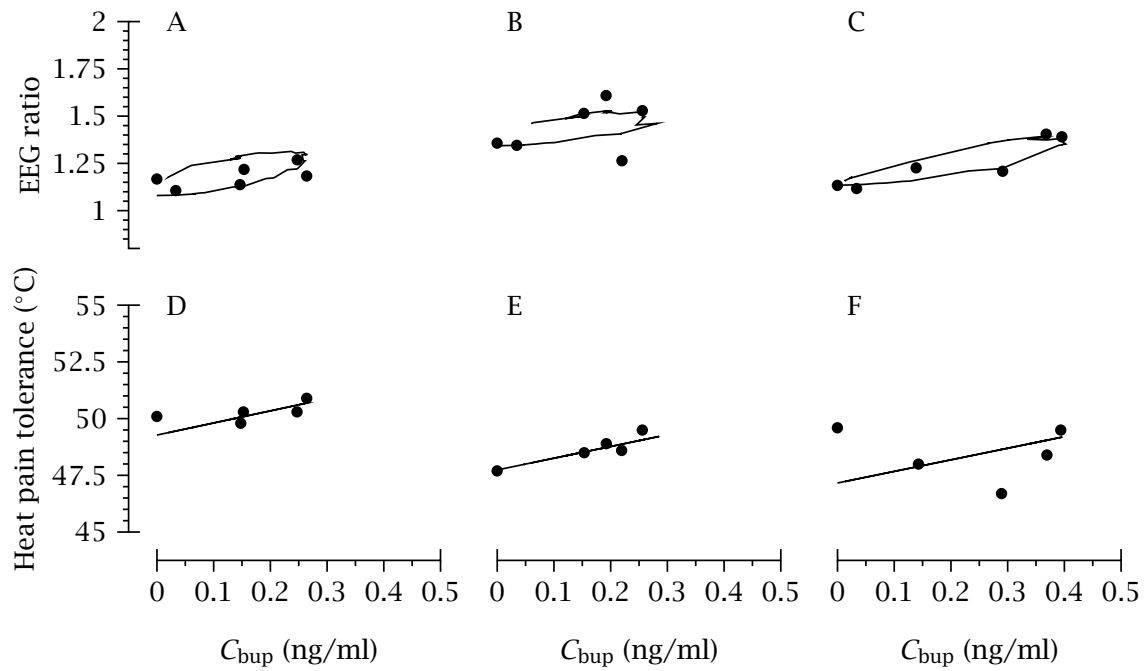
The EEG ratio was more sensitive to buprenorphine than skin pain tolerance, with a  $10 \pm 3$  (mean  $\pm$  SE) times greater potency: resting EEG ratio  $C_{100} = 0.90 \pm 0.10$  ng/mL *versus* EEG ratio  $C_{100} = 9.01 \pm 1.90$  ng/mL. To get an indication of whether the EEG is a good predictor of heat pain tolerance, the 2 PD models were coupled via their corresponding plasma concentrations (obtained from taking the measurement variability  $\sigma$ , into account). Figure 4.11 shows that the EEG predicts heat pain tolerance with acceptable uncertainty compared with the skin test when coupling the PD models to their corresponding plasma concentrations.

## 4.3 Discussion

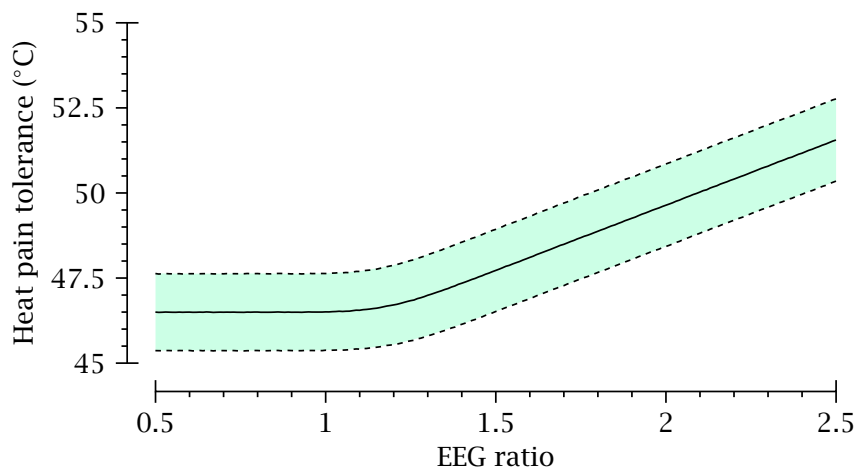
Our main findings are that the EEG ratio can be used as a surrogate measure of buprenorphine effect and that the SPKPD analysis, which includes tracking and update features, allowed the computation of the time-dependent variability in drug absorption from patch to blood. Both results confirm our study hypotheses. We demonstrated that buprenorphine's absorption varied over time, ranging from -40% to +60% of baseline



**Figure 4.9:** Likelihood profiles showing the change in objective function *versus* a relative change in the denoted parameter (A-I) while estimating the remaining parameters. The dashed line denotes a change of 3.84 points in objective function (OFV), indicating the  $P = 0.05$  level. The crossings of the likelihood profiles with the dashed lines give a parameter range corresponding to a 95% confidence interval. (A)  $k_a$  is the buprenorphine absorption rate; (B)  $k_e$  is the buprenorphine elimination rate constant; (C)  $t_{1/2, k_{e0}}$  is the blood-effect-site equilibration constant; (D)  $V_d$  is the volume of distribution; (E) Baseline (BLN) is the electroencephalography (EEG) ratio baseline estimate; (F) BLN is the heat pain tolerance baseline estimate; (G)  $\sigma_w$  is the variability in the absorption rate constant in the log domain; (H)  $C_{100}$  is the effect-site concentration causing a 100% increase in EEG ratio; (I)  $C_{100}$  is the effect-site concentration causing a 100% increase in heat pain tolerance.



**Figure 4.10:** Random examples of effect *versus* plasma concentration for electroencephalography ratio (A-C) and pain tolerance (D-F). Each panel represents the data of one subject.



**Figure 4.11:** Relationship between the electroencephalography ratio and heat pain tolerance as derived from the 2 stochastic pharmacokinetic-pharmacodynamic (SPKPD) analyses. Shown is the median  $\pm$  1 SD.



absorption, and that buprenorphine's effect on the EEG ratio is 10 times more sensitive than buprenorphine's effect on dulling noxious skin stimuli.

### 4.3.1 Variations in Absorption Rate

The heat pain tolerance data were previously analyzed by Andresen et al.<sup>6</sup> The input to their PD model consisted of cubic splines fitted to the measured concentrations because no PK model could be found to adequately describe transdermal drug delivery. Although splines give smooth curves, they cannot correct for measurement error, which may result in possibly amplified errors of the interpolated values. Although the structural PK model that we applied may be simple, it provides the PD model with interpolated concentration values based on best estimates of drug absorption and disposition at the sampling times of the effect parameters.

Tornøe *et al.*<sup>89</sup> were the first to model subcutaneous drug absorption with a varying absorption rate. In the current study, we analyzed transdermal drug absorption using an approach similar to theirs. Assuming that the release of drug from the patch is constant over time, variations in drug absorption from the skin may be related to diurnal changes in local skin blood flow because of fluctuations in skin temperature, cardiac output, and ambient temperature. For example, the drug label for buprenorphine warns patients to avoid exposing the patch to external heat. For the fentanyl transdermal patch, heat-related toxicity has been described and was related to a significant (25%-30%) increase in plasma fentanyl concentration because of an increased drug release from the patch.<sup>56</sup> In our study, it is unknown whether the  $k_a$  fluctuations affected our PD outcome significantly. Theoretically, quantifying the fluctuations in  $k_a$  by modeling, the process noise could increase the precision of the estimate of the onset and offset of effect. However, the design of our study prohibited the precise estimation of  $t_{1/2, k_{e0}}$ . For heat pain tolerance, no hysteresis between plasma concentration and effect was detected, and for EEG ratio, the log-likelihood profile of  $t_{1/2, k_{e0}}$  exhibits a rather large 95% confidence interval (12-48 hours), indicating that the support for hysteresis is limited. Still, excluding this parameter from the model had a significant negative effect on the objective function value, which suggests that the slow distribution of buprenorphine from plasma to brain is detectable in the EEG data. It is of interest to note that Andresen *et al.*<sup>6</sup> found a direct and linear effect of buprenorphine on heat pain tolerance similar to our observations.

### 4.3.2 EEG Ratio as Biomarker of Opioid Effect

The response to skin heat pain test is quite subjective, whereas the resting EEG is a more objective measure of drug effect.<sup>59</sup> This is the first study to assess the effect of the long-term administration of an opioid on the EEG and particularly on the EEG ratio. Most studies on the effect of opioids on resting EEG use Fast Fourier Transform to convert the raw EEG signal into quantifiable measures, such as spectral edge and median frequency.<sup>49</sup> Several of these studies show that slowing of the frequency of the EEG reflects a narcotic or sedative drug effect.<sup>46,49,73,66</sup> In the current study, a CWT was used to extract information from the raw EEG signal, followed by the evaluation of multiple frequency bands combined in a single EEG ratio. The design of the wavelet

analysis was chosen to be comparable with previous studies on analgesic effect and resting EEG.<sup>35,34</sup>

The rationale for using an EEG ratio is that opioids produce high-voltage cortical bursts associated with increases in EEG spectral power in predominantly the low-frequency range (0-10 Hz).<sup>99</sup> However, the frequency-specific alterations in cortical EEG oscillations depend on the receptor type that is activated.<sup>99</sup> Because buprenorphine is a mixed agonist-antagonist opioid receptor modulator (*i.e.*, acting at multiple opioid receptors), it seems more rational to assess the entire frequency range rather than the individual frequency bands independently. In addition, because the EEG power between subjects varies considerably, opioids may cause larger effects in some subjects (*e.g.*, subjects with an initial higher power). Using the ratio of the normalized EEG spectral distribution partly cancels out such bias, as the EEG ratio assesses the relative distribution between low- and high-frequency oscillations and quantifies how this balance is altered by buprenorphine administration in comparison with placebo treatment.

An interesting observation in our study is that the resting EEG effects were more sensitive to buprenorphine than the pain responses, with just one-tenth of the concentration at the effect-site required for a doubling of effect ( $C_{100}$ ). This makes the EEG ratio an attractive biomarker of opioid effect compared with pain intensity testing when measuring the PD of opioid analgesics, especially when long-term administrations are tested.

The findings on the effect of buprenorphine on the resting EEG ratio were obtained in healthy male volunteers without coadministration of sedative hypnotic agents. For clinical use, it would be interesting to investigate in future studies whether the ratio would still be detectable in the presence of a potent IV or inhaled anesthetic agent. Although the mechanisms behind coadministration are not yet understood, several recent studies have been focused on this topic. Liley *et al.*<sup>48</sup> used a fixed-order autoregressive moving average model to analyze EEG signals from 2 frontal electrodes and found that during the simultaneous administration of remifentanyl and propofol, increasing remifentanyl concentrations caused significant changes in the cortical EEG. In line with this, Kortelainen *et al.*<sup>47</sup> used the frequency spectrum from the Fz channel to separate the effects of propofol and remifentanyl and found the entire frequency range from 2 to 20 Hz to contribute to the remifentanyl effect, although the low frequencies from 1 to 5 Hz showed the most discriminative oscillations.

## 4.4 Conclusions

In this study, the effect of transdermal buprenorphine on the cortical EEG (EEG ratio) and on heat pain tolerance was investigated; the EEG ratio was defined as (% slow frequency bands, 0-10.5 Hz)/(% fast frequency bands, 10.5-32 Hz). We showed that the EEG ratio is a reliable surrogate measure of buprenorphine effect, with a 10-fold greater sensitivity than heat pain tolerance. In addition, we successfully analyzed the data with a SPKPD model that allowed us to compute the time-dependent variability in drug absorption from patch to skin. The analysis showed a high variability in absorption, possibly related to diurnal variations in skin blood flow.

