ANESTHESIOLOGY

Pharmacokinetics and Pharmacodynamics of Remimazolam (CNS 7056) after Continuous Infusion in Healthy Male Volunteers

Part II. Pharmacodynamics of Electroencephalogram Effects

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Intravenously administered remimazolam can produce deep sedation quickly from which the patient recovers rapidly due, in part, to its relatively high clearance by tissue esterases
- Electroencephalogram measures with a significant correlation to sedation scales provide a continuous noninvasive method for quantifying central nervous system drug effects without the need to stimulate the patient

What This Article Tells Us That Is New

- Electroencephalogram changes during remimazolam infusion in 20 adult male volunteers were characterized by an initial increase in the beta frequency band and a late increase in the delta frequency band
- Beta ratio had a monotonic relationship to Modified Observer's Assessment of Alertness and Sedation scores and could be modeled using a standard sigmoid E_{max} pharmacodynamic model
- The standard sigmoid E_{max} model failed to describe the time course of the Narcotrend Index appropriately; it was necessary to extend the model by adding a second sigmoid term with a second effect site concentration

ABSTRACT

Background: Remimazolam (CNS 7056) is a new ultra-short acting benzodiazepine for IV sedation. This study aimed to investigate the electroencephalogram (EEG) pharmacodynamics of remimazolam infusion.

Methods: Twenty healthy male volunteers received remimazolam as continuous IV infusion of 5 mg/min for 5 min, 3 mg/min for the next 15 min, and 1 mg/min for further 15 min. Continuous EEG monitoring was performed by a neurophysiologic system with electrodes placed at F3, F4, C3, C4, O1, O2, Cz, and Fp1 (10/20 system) and using the Narcotrend Index. Sedation was assessed clinically by using the Modified Observer's Assessment of Alertness and Sedation scale. Pharmacodynamic models were developed for selected EEG variables and Narcotrend Index.

Results: EEG changes during remimazolam infusion were characterized by an initial increase in beta frequency band and a late increase in delta frequency band. The EEG beta ratio showed a prediction probability of Modified Observer's Assessment of Alertness and Sedation score of 0.79, and could be modeled successfully using a standard sigmoid E_{max} model. Narcotrend Index showed a prediction probability of Modified Observer's Assessment of Alertness and Sedation score of 0.74. The time course of Narcotrend Index was described by an extended sigmoid E_{max} model with two sigmoid terms and different plasma–effect equilibration times.

Conclusions: Beta ratio was identified as a suitable EEG variable for monitoring remimazolam sedation. Narcotrend Index appeared less suitable than the beta ratio for monitoring the sedative effect if remimazolam is administered alone.

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The new benzodiazepine remimazolam (CNS 7056; PAION UK Ltd., United Kingdom) is an ester-based drug that is rapidly hydrolyzed in the body by tissue esterases to an inactive metabolite.[1] In a previous phase I study in volunteers, remimazolam was shown to produce deep sedation with fast onset and recovery due to a relatively high clearance, a small steady state volume of distribution, and a short elimination half-life.[2]

A preclinical study in sheep assessed electroencephalogram (EEG) changes produced by remimazolam, midazolam, and propofol, and reported a higher magnitude of alpha power for remimazolam and propofol than for midazolam.[3] Further, no burst suppression patterns or isoelectric EEG was observed for remimazolam. The relationship between the arterial blood concentration of remimazolam and the EEG alpha power as effect variable could be successfully modeled by a sigmoid E_{max} model in another preclinical study.[4] However, the estimated concentration–effect relationship was very steep (Hill coefficient, 5.2).

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The pharmacokinetic–pharmacodynamic models developed from volunteer data related the estimated remimazolam effect site concentrations to the Bispectral Index (BIS) of the EEG and to the Modified Observer's Assessment of Alertness and Sedation scale as clinical measure of sedation.[5] However, these models had some limitations which are partly described in the first part of this work. Regarding the EEG analysis, the BIS index was originally developed for propofol, and it has been reported that the correlation between depth of sedation and the BIS index was weaker for the benzodiazepine agonist midazolam than for propofol.[6]

The Narcotrend Index is a EEG measure designed to assess the depth of sedation and anesthesia.[7] Multiple clinical and validation studies are described using the Narcotrend Index, including the sedative effect of midazolam, as well as comparisons with the BIS index.[8] Therefore, one can assume that the Narcotrend Index may also reflect the sedative effect of remimazolam.

This part of the work investigated the remimazolam-induced changes in the spontaneous EEG recorded continuously from multiple electrode positions in order to identify suitable EEG variables for monitoring the depth of sedation. In addition, the suitability of Narcotrend Index for monitoring remimazolam-induced sedation was assessed. Pharmacodynamic models for both the selected EEG variable and the Narcotrend Index were developed and their predictive performance was assessed.

Materials and Methods

Study Conduct, Subjects, and Protocol

This was a prospective, open-label, randomized, two-arm, single-center, crossover, phase 1 clinical trial performed in accordance with the guidelines for Good Clinical Practice and the Declaration of Helsinki. The study was approved by the local ethics committee on May 12, 2017 (ethics committee of the Medical Faculty of the Friedrich-Alexander-University Erlangen-Nürnberg, Erlangen, Germany; reference No. AZ113_17). The trial was registered to the EudraCT database (No. 2017-000455-12). Consolidated Standards of Reporting Trials guidelines were followed and the study was clinically monitored by the Center for Clinical Studies Erlangen (Erlangen, Germany). The trial took place at the Department of Anesthesiology of the University Hospital Erlangen (Erlangen, Germany) between July and October 2017.

Details of the clinical protocol are described in detail in the accompanying Part I of this study. In order to limit potential sources of interindividual variability such as age, weight, and sex, the study was conducted in a relatively homogenous population with the following inclusion criteria: healthy male volunteers between 18 and 40 yr, body weight between 60 and 100 kg, body mass index between 20 and 30 kg/m^2, and an American Society of Anesthesiologists Physical Status classification of I. After written informed consent was obtained, the volunteers received remimazolam as continuous IV infusion with an infusion rate of 5 mg/min for the first 5 min, 3 mg/min for the next 15 min, and 1 mg/min for the last 15 min. Arterial blood samples were taken frequently at predefined times up to 6 h after infusion was stopped. Sedation was assessed every 2 min using the Modified Observer's Assessment of Alertness and Sedation scale, starting immediately before remimazolam infusion until the volunteers regained full alertness. The time to loss-of-consciousness was defined as the time to the first Modified Observer's Assessment of Alertness and Sedation score that was less than or equal to 1. The time to regained consciousness was defined as the time to the first of the three subsequent Modified Observer's Assessment of Alertness and Sedation scores of 5 after the stop of remimazolam administration.

Multichannel EEG Recording and Processing

The raw EEG signals from six channels were recorded with a neurophysiologic system (Natus-Nicolet V32 with Neuroworks software 8.4.0; Natus Europe, Germany). The skin was prepared with abrasive gel (Everi; GVB-geliMED, Germany) to keep impedances less than 10 kΩ. Using an EEG cap (MultiCap Base; GVB-geliMED), reusable sintered Ag/AgCl electrodes (GVB-geliMED) were placed at the following positions according to the international 10/20 system: F3, F4, C3, C4, O1, O2, Cz (common reference), and Fp1 (ground). A conductive gel (Neurgel; GVB-geliMED) was injected through the cup electrodes. The analog EEG signal was digitized at a rate of 500 Hz by the Natus software and stored on hard disk for further processing.

The raw digitized EEG signals of each EEG channel were first low-pass filtered *via* a finite impulse response filter at 47 Hz, then down sampled to 125 Hz, and subsequently high-pass filtered with a finite impulse response filter at 0.5 Hz (Matlab Signal Processing Toolbox, release 6.2; Math-Works Inc., USA). For EEG analysis, the preprocessed EEG signal was segmented into epochs of 8.192 s (1,024 data points) length. The EEG signal epochs were first evaluated for signal quality (automatic neural networks based artifact recognition)[9] and stationarity (*i.e.*, whether the statistical properties of the EEG signal epoch are time invariant using a nonparametric "run" test)[10] after removal of direct current offset.

Visual analysis was performed with processed EEG signals, spectrograms computed by multitaper power spectrum estimation[11] between 0.5 and 40 Hz, and power spectra from delta (0.5 to 5 Hz), theta (5 to 8 Hz), alpha (8 to 13Hz), beta (13 to 26 Hz), and gamma (26 to 47 Hz) frequency bands (frequency range from greater than the lower threshold to less than or equal to the higher threshold).[12]

Quantitative EEG analysis was performed with 38 univariate EEG variables computed in the time and frequency

domain from artifact free stationary EEG signal epochs. A detailed description of the EEG processing is presented in the section S1 of the Supplemental Digital Content of this work (http://links.lww.com/ALN/C146).

Selection of EEG Parameters for Pharmacodynamic Modeling

In order to identify suitable EEG variables for monitoring the sedative effect of remimazolam, the derived EEG variables were further analyzed with respect to signal-to-noise ratio and prediction probability[13] for Modified Observer's Assessment of Alertness and Sedation scores.

The signal-to-noise ratio was computed as the ratio between the variance of the estimated variable values and the variance of the residuals. The residuals were calculated as the difference between estimated and calculated variable values. The processing steps for estimating each EEG variable were: first, rejection of variable values from EEG epochs that were nonstationary or contaminated with artifacts; second, linear interpolation of rejected variable values; and thirdly, smoothing with Tukey running median smoother.[14] The signal-to-noise ratio was calculated from the time interval between 5 min before the first Modified Observer's Assessment of Alertness and Sedation score and 5 min after the last Modified Observer's Assessment of Alertness and Sedation score was obtained (Supplemental Digital Content S2, http://links.lww.com/ALN/C146).

The prediction probability was calculated from Modified Observer's Assessment of Alertness and Sedation scores and corresponding values of the EEG variable. The value of the EEG variable was selected as the last available value from 35 s before the Modified Observer's Assessment of Alertness and Sedation score observation to the time point upon which the Modified Observer's Assessment of Alertness and Sedation score was observed. Subsequently, the relationship between the time course of the EEG variable and the time course of the Modified Observer's Assessment of Alertness and Sedation score was visually evaluated as either concordant or discordant. A concordant relationship was present if EEG variable values and Modified Observer's Assessment of Alertness and Sedation scores were rank ordered in the same direction, and a discordant relationship was present if they were rank ordered in the opposite direction. In order to compare the prediction probability values of all EEG variables independent of their type of relationship to the Modified Observer's Assessment of Alertness and Sedation scores, the prediction probability of the EEG variable was calculated as one minus prediction probability in case of a discordant relationship (Supplemental Digital Content S2, http://links.lww.com/ALN/C146).

From EEG variables having a signal-to-noise ratio higher than the 75% quantile of the population distribution and a prediction probability value higher than the 75% quantile of the population distribution, the EEG variable showing the highest signal-to-noise ratio times prediction probability was selected for pharmacokinetic–pharmacodynamic modeling. In order to reduce the amount of EEG variable data in each volunteer, the pharmacodynamic analysis was performed with linearly interpolated values from 10 min before until 90 min after the start of remimazolam infusion, with a time resolution of 0.25 min.

Narcotrend Recording and Processing

Continuous EEG monitoring was performed using the Narcotrend Compact M monitor (MT MonitorTechnik, Germany). The skin on the volunteer's forehead was prepared with abrasive gel (Everi; GVB-geliMED) to keep impedances less than 2 kΩ, and three disposable adhesive EEG electrodes (MT MonitorTechnik) were placed on the volunteer's forehead with a distance of at least 8 cm between any two signal electrodes. The original output of the Narcotrend monitor consisted of one Narcotrend Index value every 5 sec. For pharmacodynamic modeling, the data from 10 min before until 90 min after start of infusion (*i.e.*, 55 min after stop of infusion) were used. In order to reduce the amount of Narcotrend Index values per subject and to have Narcotrend Index values at identical time points, one Narcotrend Index value was selected every 6 sec after linear interpolation of the raw data.

Pharmacokinetic–Pharmacodynamic Modeling

Pharmacokinetic–pharmacodynamic modeling was performed in a sequential approach: pharmacokinetics were analyzed first, and the individual empirical Bayesian estimates of the pharmacokinetic parameters were used in the pharmacodynamic analysis to estimate the plasma and effect site concentration at the time points where the dependent pharmacodynamic value (selected EEG variable and Narcotrend Index) was measured. The pharmacokinetic modeling of remimazolam is described in detail in the accompanying Part I of this study. Briefly, pharmacokinetics were modeled using linear mammillary two- or three-compartment models, parametrized using elimination and intercompartmental clearances, and volumes of distributions.

For the pharmacodynamic modeling of the selected EEG variable and Narcotrend Index, sigmoid inhibitory models with effect site compartment were used. The basic model of this type had the form:

$$E = E_0 - E_{max} \frac{C_E^{\gamma}}{C_E^{\gamma} + EC_{50}^{\gamma}} \text{ or} \quad (1)$$

$$E = E_0 - (E_0 - E_{min}) \frac{C_E^{\gamma}}{C_E^{\gamma} + EC_{50}^{\gamma}} \quad (2)$$

where E is the value of the EEG variable for an effect site concentration C_E, E_0 is the baseline value of the EEG variable when no drug is present, E_{max} is the maximum inhibitory effect, E_{min} is the minimum value of the EEG variable, and γ is the Hill exponent describing the steepness of the

concentration effect curve. The effect site concentration C_E was calculated from the plasma concentration C_p of remimazolam by the differential equation:

$$\frac{dC_E}{dt} = k_{e0} \cdot (C_P - C_E) \quad (3)$$

using the individual empirical Bayesian estimates of the best pharmacokinetic model for remimazolam to calculate C_P, whereby k_{e0} is the rate transfer constant between central and effect compartment.

Interindividual variability of the model parameters was modeled by normal or log-normal distributions. Residual intraindividual variability was modeled using an additive error model. Parameters were estimated using Nonlinear Mixed Effects Modeling 7.4.1 (ICON plc, Ireland) and the first-order conditional estimation method with interaction algorithm. The development, evaluation, and validation of the pharmacodynamics models are presented in detail in the section S3 of the Supplemental Digital Content of this work (http://links.lww.com/ALN/C146).

Simulations

Various simulations were performed to illustrate clinical applications of the model. Using the estimates of the pharmacokinetic parameters and effect site equilibration rate constant, we determined the time to maximum effect concentration after a bolus dose of remimazolam (T_{peak}), and the context-sensitive decrement times, *i.e.*, the time for a defined decrease (25%, 50%, and 75%) of the effect site concentration after continuous target controlled infusion of variable length.[15]

Statistics

Data are presented as median with range or as mean ± SD if not stated otherwise.

The evaluation and selection of pharmacodynamic models was based on the Nonlinear Mixed Effects Model objective function (*OFV*). Model selection was primarily based on the Bayes information criterion (*BIC*) defined as BIC = OFV + ln(Nobs) × Npar, where Nobs is the number of observations and Npar is the number of parameters to be estimated. The model with the lowest Bayes information criterion was selected as best model. The difference in the objective function between two models was further tested for significance by the chi-square test with the degree of freedom being equal to the difference in the number of model parameters. Average individual values of effect variables at baseline and at recovery were compared using the *t* test for paired samples or the Wilcoxon test. $P < 0.05$ was considered statistically significant.

For pharmacodynamic modeling, sample size was estimated by simulation. The sample size estimation is presented in detail in the Supplemental Digital Content S4 (http://links.lww.com/ALN/C146).

Results

Twenty-five subjects were screened for this study. Three subjects who provided informed consent were not eligible because of abnormal laboratory values at screening. Two subjects were further excluded: one subject due to a pretreatment vasovagal syncope during arterial cannulation and one subject due to positive urine drug screening test on the treatment day. The remaining 20 subjects received remimazolam as scheduled and completed the study successfully. The demographic data along with observed clinical endpoints are summarized in table 1.

Multichannel EEG Analysis

A total of 309 h EEG signal from six EEG referential recordings was analyzed. The average portion of EEG epochs showing nonstationarity or artifacts was 8.9 ± 5.5%, 8.8 ± 5.9%, 3.3 ± 2.4%, 2.7 ± 2.2%, 17.2 ± 13.6%, and 16.2 ± 11.1% in F3, F4, C3, C4, O1, and O2 recording, respectively. The mean absolute amplitude of the EEG voltage was higher in occipital than in frontal or central EEG recordings, and approximately two times higher during sedation than during base line (table 2).

Figure 1 depicts representative EEG epochs from one volunteer during awake (fig. 1A), deep sedation (fig. 1B), regain of consciousness (fig. 1C), and recovery (fig. 1D). There were no obvious differences in EEG patterns between left and right hemisphere recordings. No burst suppression patterns or isoelectric EEG were observed in the time domaine analysis. Figure 2 shows the spectrograms between 0.5 and 40 Hz in one volunteer who experienced loss of consciousness at 4 min after the start of remimazolam infusion and regained consciousness 21 min after the end of remimazolam administration (*i.e.*, at 56 min after infusion start). During the awake state before remimazolam infusion, spectral power is clearly present around 11 Hz in occipital recordings. Shortly after start of remimazolam infusion, a clear initial increase in power between 10 and 30 Hz can be observed in frontal, central and occipital recordings, followed by a subsequent power decrease in this frequency range. After the stop of infusion (*i.e.*, after 35 min after start of remimazolam administration), the spectral power in this frequency range decreased gradually until shortly before consciousness was regained, when it slightly raised again. During remimazolam infusion, power at frequencies lower

Table 1. Demographic Data and Clinical Endpoints

Age (yr)	25 ± 4 (20–38)
Weight (kg)	77 ± 10 (64–99)
Height (cm)	179 ± 8 (169–197)
Body mass index (kg/m^2)	24 ± 2 (21–29)
Loss of consciousness (min)	5 ± 1 (4–8)
Regain of consciousness (min)	54 ± 7 (42–68)

Data are presented as mean ± SD (range).

Table 2. Absolute Amplitude of Electroencephalogram Voltage

Recording	Baseline (μV)	Sedation (μV)	Recovery (μV)
C3	5 ± 3	9 ± 3	7 ± 3
C4	5 ± 2	9 ± 3	7 ± 3
F3	8 ± 3	15 ± 5	10 ± 5
F4	8 ± 4	15 ± 7	10 ± 6
O1	10 ± 4	18 ± 8	16 ± 14
O2	10 ± 4	18 ± 9	13 ± 7

Data are presented as mean ± SD.

than 5 Hz increased clearly about the end of remimazolam infusion. An increased power at frequencies lower than 5 Hz during the awake state may have been caused by artifacts (*e.g.*, eyeball or head movements).

The time course of average power changes in different frequency bands is depicted in figure 3. The increase in beta power shortly after start of remimazolam infusion is clearly present in all recordings. The power increase in the delta band was more pronounced in occipital than frontal recordings, whereas the power increase in the alpha and theta band was more pronounced in frontal than occipital recordings. Overall, the magnitude of power in central recordings was lower than in frontal or occipital recordings.

Selection of EEG Parameters

A total of 4,560 signal-to-noise ratios and 4,560 prediction probability values were calculated for 38 EEG variables from 20 volunteers in each of the six EEG channels. Population values were calculated for each EEG variable as mean values over individual signal-to-noise ratios and prediction probability values for each EEG channel, (*i.e.*, 228 signal-to-noise ratios and 228 prediction probability values).

Table 3 shows EEG variables that had signal-to-noise ratios and prediction probability values higher than the 75% quantile of the corresponding population distributions. These are mainly EEG variables based on power in the frequency range above 8 Hz from frontal EEG channels. The beta ratio recorded from electrode position F3 showed the highest signal-to-noise ratio (4.29) and one of the highest Modified Observer's Assessment of Alertness and Sedation prediction probability of 0.79 (figure S5F1A of the Supplemental Digital Content S5, http://links.lww.com/ALN/C146). Thus, it was selected for further pharmacokinetic-pharmacodynamic modeling.

EEG Beta Ratio

The average value of beta ratio before start of remimazolam infusion was −0.84 ± 0.92 (mean ± SD). After start of remimazolam infusion, beta-ratio decreased to a minimum value of −4.10 ± 0.54, and showed a plateau during further infusion with a slight increase in the last minutes of infusion. During the last 10 min of the observation period (*i.e.*, between min 45 and 55 after remimazolam infusion), an average value of −1.56 ± 0.72 was regained ($P < 0.001$ compared to baseline).

The complete data set used for pharmacodynamic modeling consisted of 8,019 beta ratio values. A standard sigmoid model as shown equation 2 was fitted to the data. The individual parameters of the best pharmacokinetic model of remimazolam were used to calculate the plasma and effect site concentrations. This model showed already a quite high goodness of fit without any bias and relatively small prediction errors. Therefore, the basic model without covariates was accepted as the best model (see model predictions and diagnostic plots in the section S6 of the Supplemental Digital Content of this work, http://links.lww.com/ALN/C146). Table 4 summarizes the parameter estimates and figure 4 depicts the visual predictive check for the final model (fig. 4A) along with the time course of model predicted remimazolam effect site concentrations (fig. 4B). Figure 5 shows the concentration–effect relationship of remimazolam as simulated with the standard sigmoid model described previously. The context-sensitive decrement times for the effect site concentration were simulated using the estimates of the effect site equilibration rate constant and the parameters of the best pharmacokinetic model of remimazolam (fig. 6). The context-sensitive halftime after 4 h of remimazolam infusion was 11.0 ± 2.5 min. The simulated time to maximum effect site concentration after a bolus dose of remimazolam was 2.6 ± 0.5 min.

Narcotrend Index

The data set used for pharmacodynamic modeling consisted of 1,001 Narcotrend Index values for each subject, from 10 min before until 90 min after the start of infusion, with a time resolution of 0.1 min. Figure 7 shows the individual time courses of the Narcotrend Index. The average baseline value of Narcotrend Index before start of remimazolam infusion was 96.1 ± 3.5 (mean ± SD). The baseline level was approximately regained at the end of the recording, with an average value of 91.2 ± 6.1 during the last 10 min ($P < 0.001$ compared to baseline). The minimum achieved Narcotrend Index value was characterized by a large inter-individual variation with values between 24 and 66.

Narcotrend Index and Modified Observer's Assessment of Alertness and Sedation score did not show a concordant relationship. The volunteers reached a Modified Observer's Assessment of Alertness and Sedation score of less than or equal to 1 within the first 10 min when the Narcotrend Index was around 80. At the end of infusion, the median Modified Observer's Assessment of Alertness and Sedation score was also 1, whereas the Narcotrend Index revealed a value of about 50. This resulted in a median prediction probability of Modified Observer's Assessment of Alertness and Sedation scores for the Narcotrend Index of 0.74 (figure S5F1B of the Supplemental Digital Content S5, http://links.lww.com/ALN/C146).

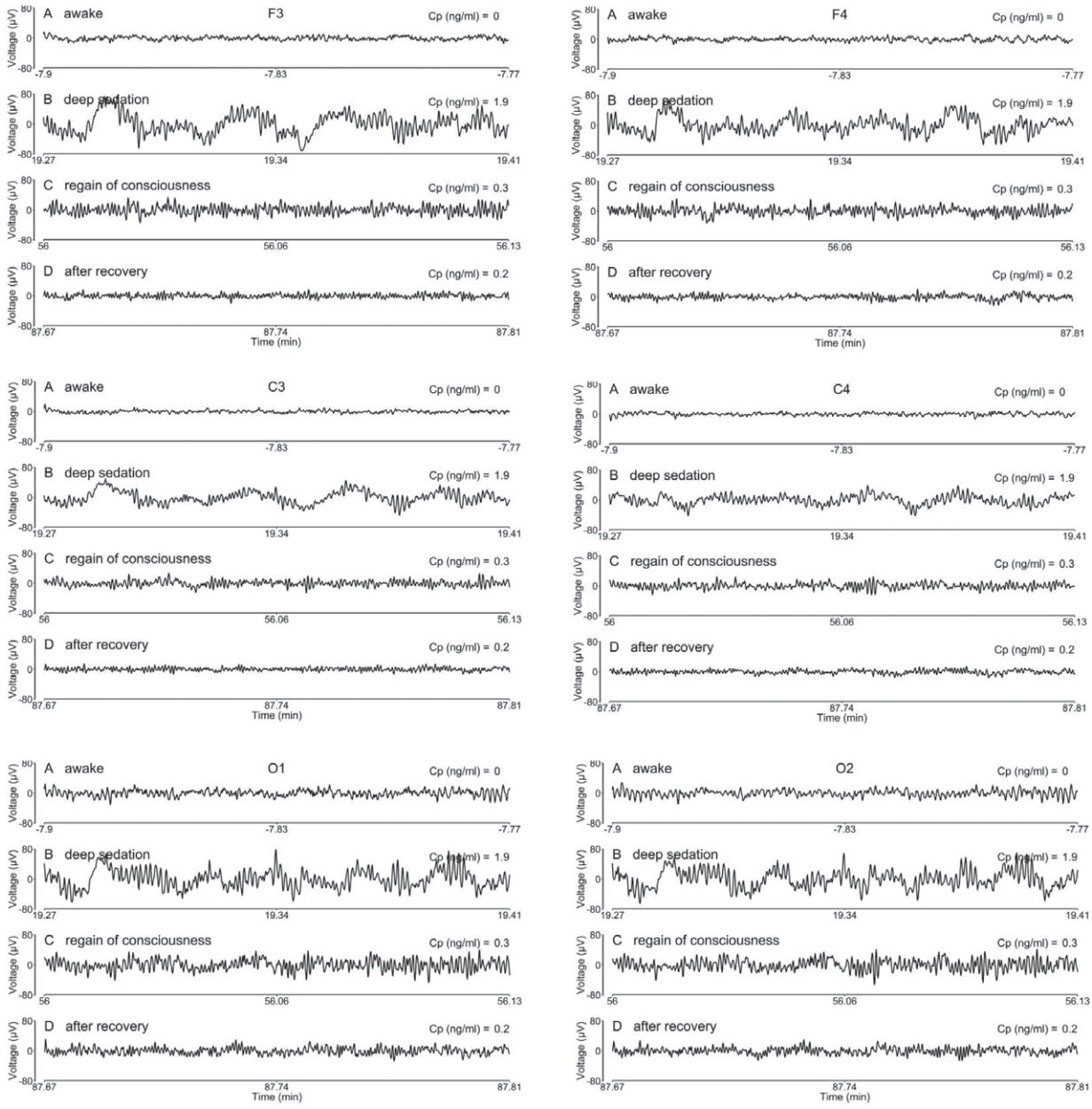

Fig. 1. Electroencephalogram epochs from one volunteer during awake state (*A*), deep sedation (*B*), regain of consciousness (*C*), and after recovery (*D*) from frontal (F3, F4, *top*), central (C3, C4, *middle*), and occipital (O1, O2, *bottom*) recordings. Time in relation to start of remimazolam administration. Cp, pharmacokinetic model predicted concentration of remimazolam.

Standard and extended sigmoid models were fitted to the data. The individual parameters of the best pharmacokinetic model of remimazolam were used to calculate the plasma and effect site concentrations.

In most volunteers, the time course of the Narcotrend Index showed two phases: an initial sharp decrease to a plateau with values between 70 and 80 during the first 20 min after start of infusion, followed by a slower decrease to values of about 40 to 50, with the minimum reached about 5 min after the stop of infusion. Due to this behavior, the standard sigmoid E_{max} model failed to describe the time course of the Narcotrend Index appropriately. Therefore, we extended the standard sigmoid model by adding a second sigmoid term with a second effect site concentration:

$$E = E_0 - E_{max,1}\frac{C_{E,1}^{\gamma 1}}{C_{E1}^{\gamma 1} + EC_{50,1}^{\gamma 1}} - (E_0 - E_{max,1} - E_{min})\frac{C_{E,2}^{\gamma 2}}{C_{E2}^{\gamma 2} + EC_{50,2}^{\gamma 2}} \quad (4)$$

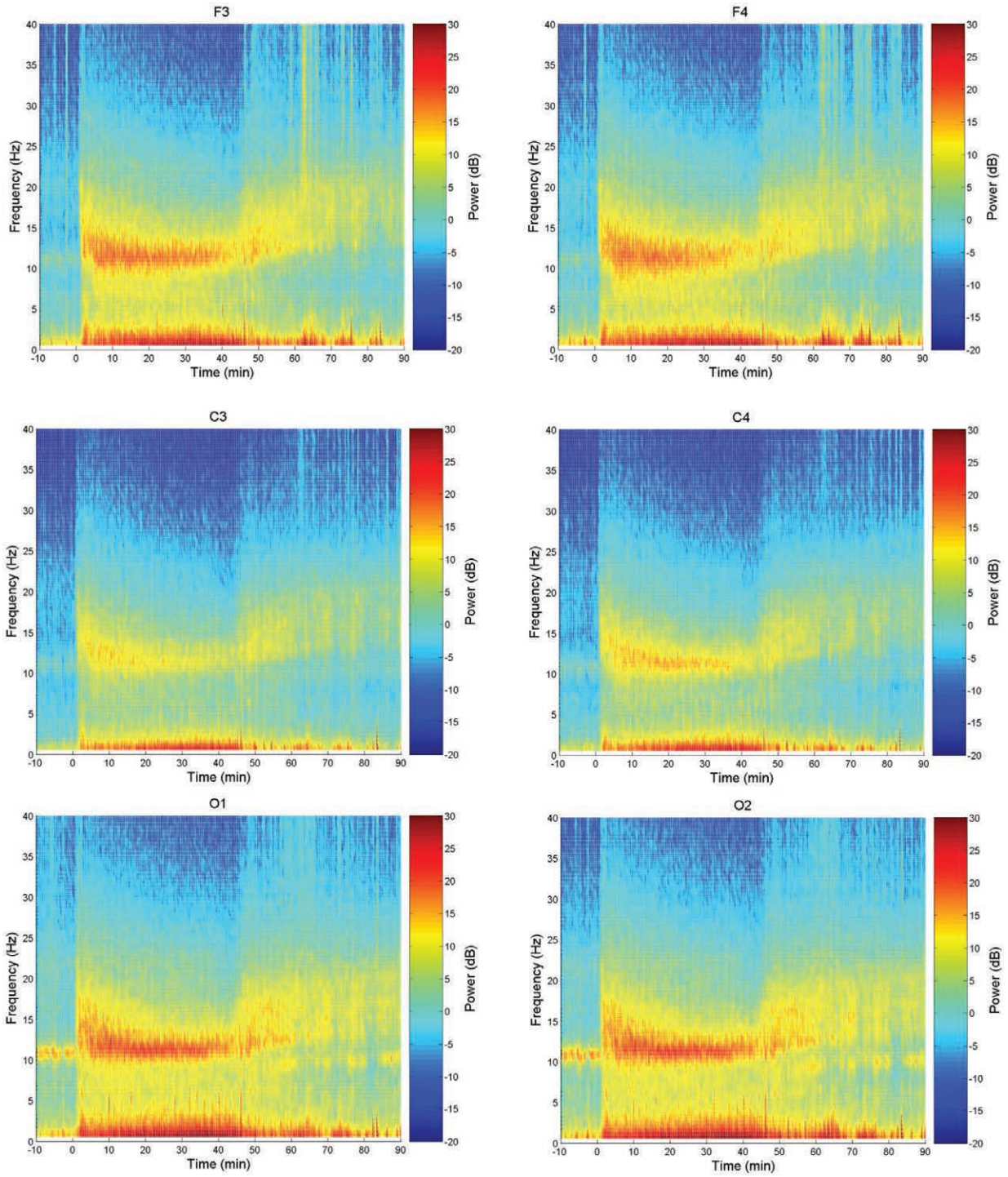

Fig. 2. Spectrograms between 0.5 and 40 Hz of one volunteer from frontal (F3, F4, *top*), central (C3, C4, *middle*), and occipital (O1, O2, *bottom*) electroencephalogram recordings. Time in relation to start of remimazolam administration.

$$\frac{dC_{E,1}}{dt} = k_{e0,1} \cdot (C_P - C_{E,1}) \quad (5)$$

$$\frac{dC_{E,2}}{dt} = k_{e0,2} \cdot (C_P - C_{E,2}) \quad (6)$$

Here, $E_{max,1}$ defines the decrease of Narcotrend Index during the initial phase, when $C_{E,2}$ is less than $EC_{50,2}$, whereas E_{min} defines the lowest possible Narcotrend Index value when both $C_{E,1}$ and $C_{E,2}$ are very high. Figure 8 shows in a typical case the measured and predicted Narcotrend Index values

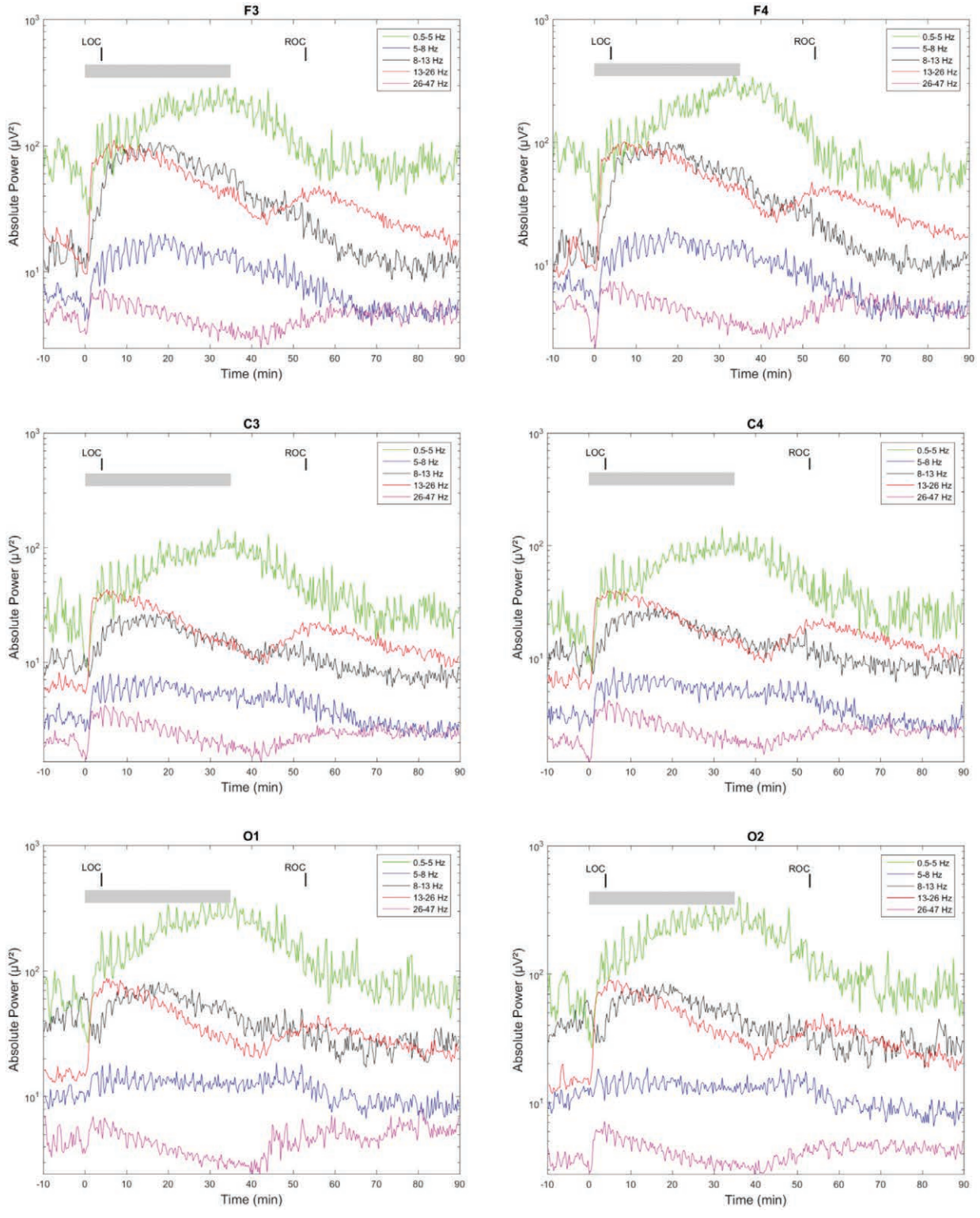

Fig. 3. Average electroencephalogram power of different frequency bands from frontal (F3, F4, *top*), central (C3, C4, *middle*), and occipital (O1, O2, *bottom*) electroencephalogram recordings from 20 volunteers. Remimazolam infusion is depicted as a *gray horizontal bar*. Time in relation to start of remimazolam administration. LOC, average loss of consciousness; ROC, average regain of consciousness.

Table 3. Electroencephalogram Variables with Highest Signal-to-Noise Ratio and Prediction Probability of Modified Observer's Assessment of Alertness and Sedation Scores

Variable	Recording	Specification	SNR	P_k	SNR × P_k
beta_ratio	F3	Log ratio power 30–47 Hz to power 11–20 Hz	4.29	0.79	3.39
beta_ratio	O1	Log ratio power 30–47 Hz to power 11–20 Hz	4.21	0.79	3.33
beta_ratio	F4	Log ratio power 30–47 Hz to power 11–20 Hz	4.04	0.8	3.23
abr	O1	Ratio power 32–47 Hz to power 8–13 Hz	3.68	0.76	2.8
abr	F3	Ratio power 32–47 Hz to power 8–13 Hz	3.48	0.8	2.78
abr	F4	Ratio power 32–47 Hz to power 8–13 Hz	3.26	0.79	2.58
symbentrop	F4	Symbolic entropy of voltage	3.0	0.82	2.46
beta_ratio	O2	Log ratio power 30–47 Hz to power 11–20 Hz	2.78	0.74	2.06
symbentrop	F3	Symbolic entropy of voltage	2.4	0.83	1.99
q95	F3	95th quantile of power distribution	2.22	0.77	1.71
symbentrop	C4	Symbolic entropy of voltage	2.11	0.8	1.69
dbr	F4	Ratio power 32–47 Hz to power 0.5–2 Hz	2.0	0.76	1.52
rel32-47	O1	Ratio power 32–47 Hz to power 0.5–47 Hz	1.95	0.77	1.5
tbr1	O1	Ratio power 32–47 Hz to power 2–5 Hz	1.97	0.76	1.5
symbentrop	C3	Symbolic entropy of voltage	1.87	0.79	1.48
dbr	C4	Ratio power 32–47 Hz to power 0.5–2 Hz	1.96	0.75	1.47
q95	F4	95th quantile of power distribution	1.86	0.77	1.43
dbr	C3	Ratio power 32–47 Hz to power 0.5–2 Hz	1.8	0.75	1.35
q95	C4	95th quantile of power distribution	1.74	0.75	1.31
ae1	F4	Approximate entropy	1.68	0.77	1.29
bispec_sfs	F4	Log ratio of sum of bispectrum 0.5–47 Hz to sum of bispectrum 40–47 Hz	1.65	0.78	1.29
rel20-26	F3	Ratio power 20–26 Hz to power 0.5–47 Hz	1.64	0.75	1.23

P_k, prediction probability; SNR, signal-to-noise ratio.

Table 4. Parameter Estimates for the Final Pharmacodynamic Model of Beta Ratio

	Population Fit					Bootstrap Analysis (956 Successful Runs)		
Parameter	Estimate	SE	RSE	Lower 95% CI	Upper 95% CI	Median	Lower 95% CI	Upper 95% CI
E_0	–0.84	0.2	23.5%	–1.23	–0.45	–0.85	–1.24	–0.45
E_{min}	–3.97	0.16	4.1%	–4.3	–3.66	–3.97	–4.32	–3.67
EC_{50} (ng/ml)	284	24.4	8.6%	236.2	331.8	286.2	240.8	344.3
γ	2.0	0.24	12%	1.53	2.47	1.98	1.6	2.49
k_{e0} (min^{-1})	0.33	0.03	8.8%	0.27	0.39	0.33	0.27	0.39
ω^2_{E0}	0.76	0.22	29.3%	0.33	1.20	0.72	0.34	1.18
ω^2_{Emin}	0.49	0.17	35.2%	0.15	0.82	0.44	0.18	0.79
ω^2_{EC50}	0.13	0.04	30.4%	0.05	0.21	0.12	0.06	0.22
ω^2_{γ}	0.22	0.06	28.1%	0.1	0.33	0.20	0.09	0.34
ω^2_{ke0}	0.12	0.05	40%	0.03	0.21	0.11	0.03	0.21
σ^2	0.12	0.02	16.4%	0.08	0.16	0.12	0.09	0.17

γ, steepness of the concentration-effect curve; ω^2, variance of interindividual errors; σ^2, variance of the residual intraindividual error; E_0, baseline value; E_{min}, minimum value of beta ratio; EC_{50}, half-maximum effect site concentration; k_{e0}, effect site equilibration rate constant; RSE, relative standard error; SE, standard error of the estimate.

of the standard and the extended model together with the predicted plasma and effect site concentrations, obtained from single-subject fit. The two phases of the Narcotrend Index time course were appropriately described by the extended model, but not by the standard sigmoid model. The two effect site concentrations $C_{E,1}$ and $C_{E,2}$ were characterized by a fast equilibration for $C_{E,1}$ and a slow equilibration for $C_{E,2}$ (table S7T1 of the Supplemental Digital Content S7, http://links.lww.com/ALN/C146).

When performing a population analysis Nonlinear Mixed Effects Modeling had problems to estimate the model parameters reliably. As the Narcotrend Index data were sampled in a rich design with about 1,000 values per subject, it was, however, possible to perform single subject fits to obtain individual parameter estimates. The best population fit was obtained when all interindividual variances were set to zero (naïve pooled fit). There were no effects of body weight and age on the pharmacodynamic

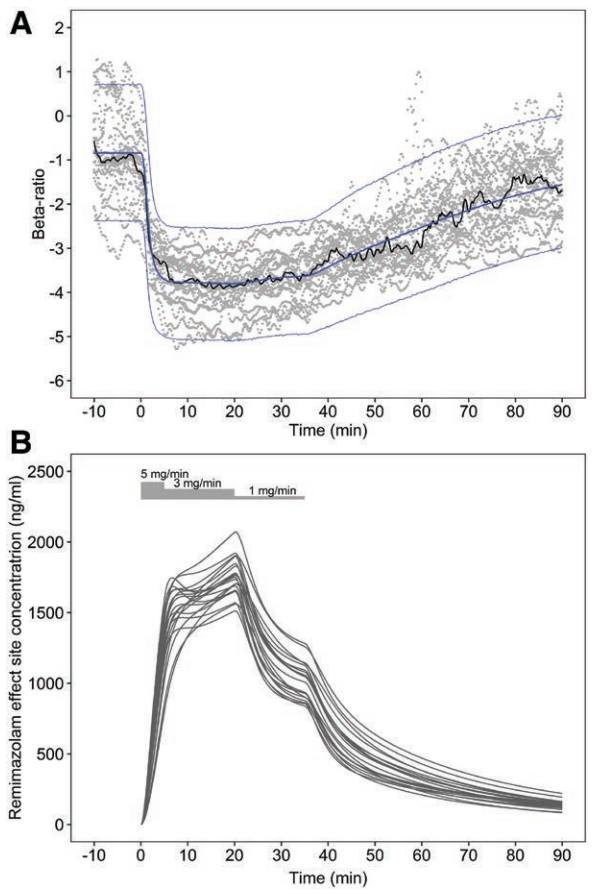

Fig. 4. Visual predictive check for the final pharmacodynamic model of beta ratio (*A*). Measured values are plotted as *gray dots*. The median of the measured beta ratio is plotted as *black line*. The *blue lines* show the 5%, 50% and 95% quantiles of the model predictions. The time course of the effect site concentration in each volunteer as predicted by the individual pharmacokinetic parameters and the individual estimates of k_{e0} is depicted in (*B*). Superimposed is the time course of remimazolam infusion. Time in relation to start of remimazolam administration. k_{e0}, effect site equilibration rate constant.

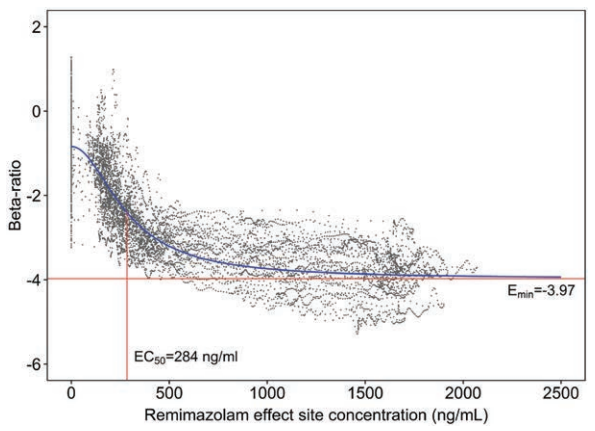

Fig. 5. Concentration–effect relationship for beta ratio as predicted by the sigmoid E_{max} model (*blue line*). Beta ratio data from each volunteer are presented as *gray dots*. E_{min}, minimum predicted value of beta ratio (*horizontal red line*); EC_{50}, remimazolam concentration at half-maximal effect (*vertical red line*).

parameters identified. The population parameter estimates of the extended pharmacodynamic model of the Narcotrend Index are presented in table 5. More detailed results of the pharmacodynamic modeling of the Narcotrend Index are given in section S7 of the Supplemental Digital Content (http://links.lww.com/ALN/C146).

Discussion

This study aimed to assess remimazolam induced changes in EEG activity and to develop EEG pharmacodynamic models of remimazolam with selected EEG measures and the Narcotrend Index as effect variables in order to characterize the concentration-sedation relationship of this drug.

A multichannel spontaneous EEG was recorded in the present study. The frontal EEG after remimazolam infusion was characterized by an initial transient increase of activity in the beta band, followed by an increase of activity in the alpha band and a delayed increase of activity in the delta band. Although the time courses of activity in gamma and theta bands were similar to those of beta and alpha bands, respectively, their magnitude was much less pronounced. Loss of consciousness occurred during the initial increase of activity in all frequency bands. After stop of remimazolam infusion, delta activity gradually decreased in all recordings. Interestingly, the recurrence of an increase in beta and gamma activity together with the return of delta activity to baseline coincides with the regain of consciousness, whereby the magnitude of the beta and gamma activity is much less pronounced at responsiveness than it is shortly after the infusion start of remimazolam (fig. 3). After stop of remimazolam infusion, the return of power in beta and gamma bands occurring simultaneously to the dissipation of power in delta and alpha bands seems to indicate the return to normal cortical activity during the awake state.

Several studies have shown that beta activity is often seen to increase during initial stages of sedation with drugs such as benzodiazepines, barbiturates, and propofol.[12,16] Veselis *et al.* report an increase in EEG activity between 13 to 30 Hz with increasing concentration of midazolam that predominantly occurred over the frontal cortex.[17] Our results agree with these findings. Interestingly, the authors found a simultaneous decrease in alpha activity mainly in occipital recordings, and that finding may have been caused by the infusion regimen or might be specifically to midazolam but not remimazolam administration. A similar increase in EEG activity between 13 to 30 Hz after midazolam infusion was also reported by Greenblatt *et al.*[18] In their investigation, maximum EEG changes were observed about 5 min after the 1-min midazolam infusion; these are similar to the

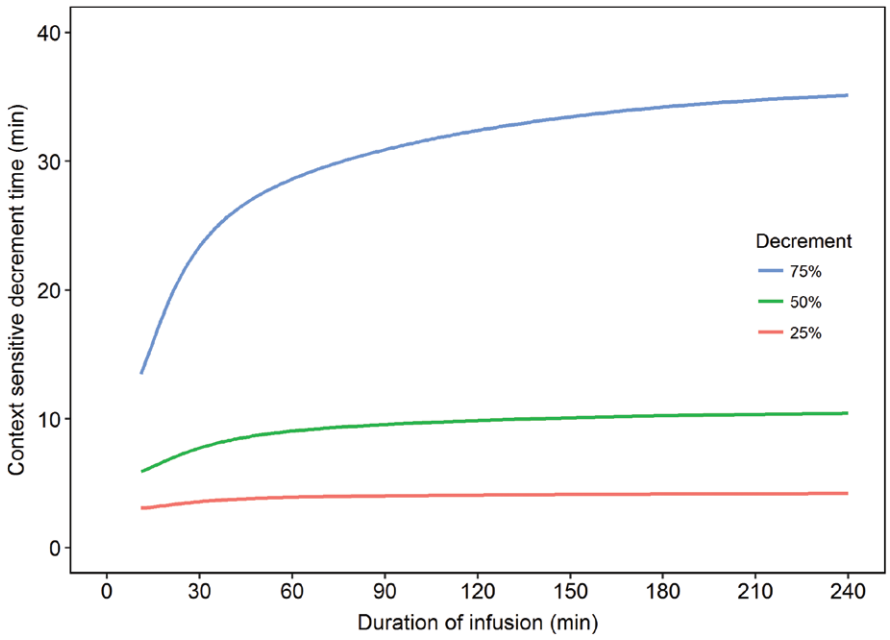

Fig. 6. Context-sensitive decrement times for the effect site concentration of beta ratio as predicted by the final pharmacodynamic and pharmacokinetic model with the typical parameter estimates for a body weight of 75 kg. Time in relation to start of remimazolam administration.

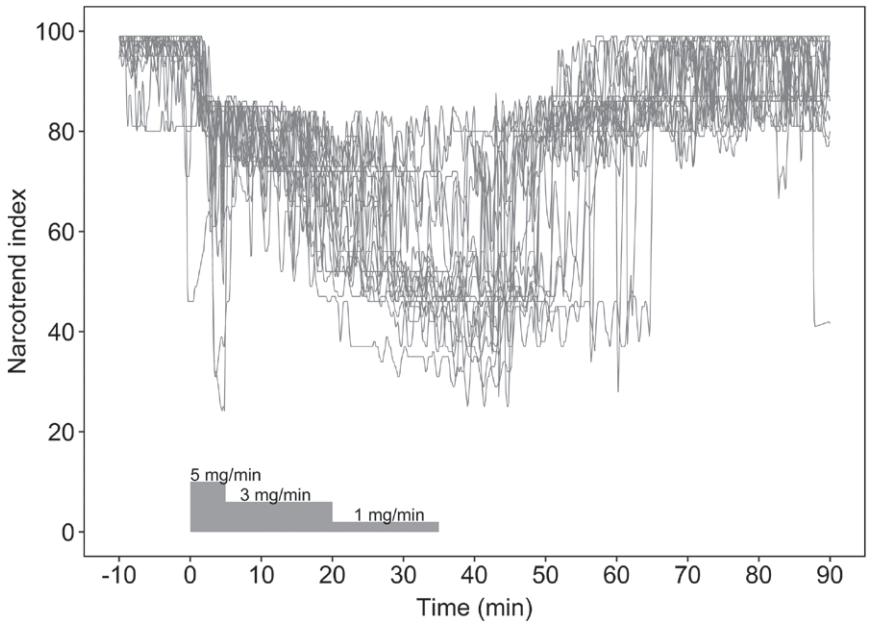

Fig. 7. Measured Narcotrend Index values. Each *gray line* represents the data of one volunteer. Superimposed is the time course of remimazolam infusion. Time in relation to start of remimazolam administration.

maximum increase in the beta frequency band after the start of remimazolam infusion in our study. In another study of nine male and nine female volunteers, a single oral dose of 5 mg of diazepam increased—regardless of sex—the absolute EEG power between 13 and 25.5 Hz, and the temporal coupling of high frequencies between hemispheres.[19]

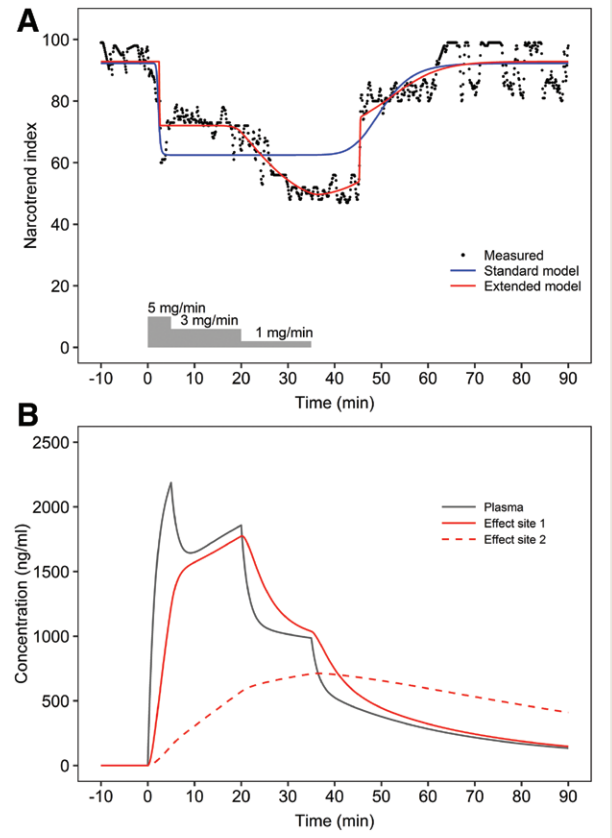

Fig. 8. Measured and predicted Narcotrend Index of one volunteer (*A*). Superimposed is the time course of remimazolam infusion. The time courses of remimazolam plasma concentration, and the effect site concentrations as predicted by the extended sigmoid model for Narcotrend Index are depicted in (*B*). Time in relation to start of remimazolam administration.

Based on the signal-to-noise ratio and the prediction probability of the Modified Observer's Assessment of Alertness and Sedation scale, the EEG variable beta ratio recorded from frontal recordings was identified as suitable for monitoring remimazolam sedation. This may not be surprising, when one considers the observed remimazolam-induced changes in beta and gamma activity. The beta ratio showed a monotonic relationship to Modified Observer's Assessment of Alertness and Sedation scores, and could be modeled successfully using a standard sigmoid E_{max} model. No covariate effects for this EEG variable were found. The relatively homogenous study population, however, should be considered. The effect site equilibration rate constant for the beta ratio was similar to the effect site equilibration rate constant for the Modified Observer's Assessment of Alertness and Sedation score (0.33 *vs.* 0.27 min^{-1}, respectively), which also indicates that the beta ratio of the EEG reflects the clinically observed sedative effect. Interestingly, the beta ratio is a variable which has an impact on the bispectral index.[20] However, in a previous study bispectral index showed a lower effect site equilibration rate constant than beta ratio (0.14 *vs.* 0.33 min^{-1}, respectively), whereas the effect site equilibration rate constant for the Modified Observer's Assessment of Alertness and Sedation scale from the previous study was comparable to that found in our study (0.25 *vs.* 0.27 min^{-1}, respectively).[5]

Breimer *et al.* used the total number of waves per second in the EEG frequency range 12 to 30 Hz as a measure of the hypnotic effect of 15 mg midazolam administered intravenously during 10 min in eight volunteers.[21] In their investigation, the equilibration time between plasma concentration and effect site was found to be 1.7 min, and the midazolam concentration corresponding to half maximum increase of the EEG measure was 290 ng/ml. In our investigation with remimazolam, the estimated value for the equilibration time was 2.1 min and the concentration to half-maximum decrease of the beta ratio was 248 ng/ml. These findings support the assumption of equivalence of the time to peak EEG effect and equipotency for the effect site concentrations between midazolam and remimazolam. The results of both our study and that of Breimer *et al.* were obtained from healthy male volunteers. Wiltshire *et al.* reported in a previous study with remimazolam that males had approximately 40% lower values of concentration for half maximum effect than females.[5] With respect to the low proportion of women in their investigation, the authors suggested that sex may be a predictor of EEG sensitivity. Further studies are needed to adequately investigate differences of remimazolam on the EEG effects between men and women.

The assessment of depth of sedation by sedation scales like the Modified Observer's Assessment of Alertness and Sedation requires frequent stimulation of the patient throughout the procedure. This stimulation can disturb the procedure or may not be adequately performed during prolonged procedures.[22] The clinical benefit of EEG measures with a significant correlation to sedation scales is that they provide a continuous noninvasive method for quantifying the central nervous system effects without the need to stimulate the patient.[21] Further clinical benefits of having EEG predictive measures were demonstrated in earlier studies. Paspatis *et al.* showed lower drug consumption[23] and van Delius *et al.* demonstrated faster recovery times[24] with care guided by processed EEG during procedural sedation with propofol. Another study in which midazolam and fentanyl were titrated to processed EEG found a significantly lower incidence of pronounced desaturation (*i.e.*, oxygen saturation less than or equal to 90%).[25]

Generally, the Narcotrend Index seemed to be less suitable as measure of the sedative effect of remimazolam. The time course of the Narcotrend Index was characterized by two phases: a fast, but relatively small, decrease to a plateau with values of about 70 to 80 within the first 20 min after the start of infusion when volunteers were in deep sedation

Table 5. Population Parameter Estimates of the Extended Pharmacodynamic Model of the Narcotrend Index

	Population Fit		Bootstrap (941 Successful Runs)		
Parameter	Estimate	RSE	Median	Lower 95% CI	Upper 95% CI
E_0	94	1.2%	94	92	96
$E_{max,1}$	17	12%	17	13	21
$EC_{50,1}$ (ng/ml)	457	9.2%	459	286	518
γ_1	10.1	48%	11.4	3.8	34
$k_{e0,1}$ (min^{-1})	0.24	17%	0.24	0.17	0.36
E_{min}	56	6.9%	55	37	61
$EC_{50,2}$ (ng/ml)	601	8.0%	609	538	876
γ_2	9.3	54%	10.7	4.3	22
$k_{e0,2}$ (min^{-1})	0.027	9.2%	0.027	0.021	0.036
σ^2	129	11%	125	98	153

All interindividual parameter variances were set to zero.

γ_1, steepness of the concentration–effect curve of the first sigmoid term; γ_2, steepness of the concentration–effect curve of the second sigmoid term; σ^2, variance of the residual intraindividual error; E_0, baseline value of the Narcotrend Index; $E_{max,1}$, maximum inhibitory effect of the first sigmoid term; E_{min}, minimum value of the Narcotrend Index; $EC_{50,1}$, half-maximum effect site concentration of the first sigmoid term; $EC_{50,2}$, half-maximum effect site concentration of the second sigmoid term; $k_{e0,1}$, first effect site equilibration rate constant; $k_{e0,2}$, second effect site equilibration rate constant; RSE, relative standard error.

(Modified Observer's Assessment of Alertness and Sedation score of less than or equal to 1), followed by a slower decrease to values of about 40 to 50, with the minimum reached about 5 min after infusion was stopped. Whether the observed two phases of the Narcotrend Index reflect a drug-specific mechanism or whether this is caused by the specific algorithm of the Narcotrend Index cannot be answered by the current study. Due to the specific behavior of the Narcotrend Index, the standard sigmoid E_{max} model failed to describe the time course of the Narcotrend Index appropriately, and it was necessary to extend the model by adding a second sigmoid term with a second effect site concentration.

A potential limitation of this study may be the dosing schedule that caused a relatively fast increase of the plasma concentration within the first 5 min after the start of remimazolam infusion. This may have caused the sequential increase in beta, alpha, and delta activity mainly observed in frontal recordings. However, the clearly slower increase in delta activity that peaked at the end of the remimazolam infusion in all recordings may represent a remimazolam EEG signature that should be investigated in further studies with different remimazolam dosing schemes. In addition, our infusion protocol may not have led to effect site concentrations to such a level so as to cause EEG burst-suppression patterns. However, neither experimental studies in sheep nor volunteer studies have reported EEG burst-suppression patterns caused by remimazolam or midazolam administration.[3–5,21]

Another limitation of the study may be the lack of steady state concentrations. Our infusion protocol produced an abrupt transition of Modified Observer's Assessment of Alertness and Sedation scores from 5 to 0 after the start of infusion, whereby Modified Observer's Assessment of Alertness and Sedation scores between 4 and 2 were transiently observed during the recovery period. This situation may have led to a lack of clear discrimination of the EEG measures for all Modified Observer's Assessment of Alertness and Sedation scores, which was reflected by a prediction probability of 0.79 and 0.74 for beta ratio and Narcotrend Index, respectively.

In conclusion, the EEG changes during remimazolam infusion were characterized by an initial increase in beta frequency band and a late increase in delta frequency band. The EEG beta ratio may be suitable for monitoring the depth of sedation during remimazolam administration, as it showed a good prediction probability of the Modified Observer's Assessment of Alertness and Sedation score, and a population pharmacodynamic model could be developed successfully using a standard E_{max} model. There were no effects of age and weight on the pharmacodynamics with respect to beta ratio. In contrast, the Narcotrend Index showed a relatively weak and discordant relationship to the Modified Observer's Assessment of Alertness and Sedation score, and therefore it might be less suitable for monitoring the sedative effect if remimazolam is administered alone.

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Competing Interests

Dr. Schüttler is scientific advisor of PAION UK Ltd. (Cambridge, United Kingdom). The other authors declare no competing interests.

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ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

Arthur Guedel's Nugget of Gold: Dislodged by One "Blade" and Snatched by Another?

Eight years at Johns Hopkins taught me many jokes contrasting "fleas" (internists, "the last to leave the carcass") with "blades" (surgeons, self-explanatory). Later, I shared these morsels of merriment with Wood Library-Museum Trustee Rod Calverley (1938 to 1995, *lower left*). In turn, Rod regaled me with stories about Dr. Arthur Guedel (1883 to 1956, *upper left*) and the latter's namesake laryngoscope (*right*), which brandished a broad blade—at a fixed acute angle—with which inexperienced laryngoscopists could easily damage patients' dental work. Over decades, Guedel fashioned low-karat scraps of dislodged dental gold into a nugget that was exhibited posthumously at his namesake museum in California. When the nugget was stolen, Rod surmised that the thief might have been "one of the students of dental surgery" who often lucubrated near the exhibit case. We mused that the gold had been dislodged by one "blade" (Guedel's) and then snatched by another…a soon-to-be surgeon. (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology.)

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