Pharmacokinetic–Pharmacodynamic Modeling of the New Steroid Hypnotic Etlanolone in Healthy Volunteers

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Background: In the last 4 y, several authors have reported largely satisfactory results using the new steroid intravenous anesthetic etlonalone (pregnanolone) to induce anesthesia. Until now, however, no investigations have addressed the infusion pharmacokinetics of etlonalone or used electroencephalographic effect data for full pharmacodynamic modeling. Thus the authors conducted a study to evaluate the pharmacokinetic and pharmacodynamic properties of etlonalone after infusion in healthy volunteers.

Methods: Etnalonone emulsion was administered to 12 healthy men using a computer-controlled infusion device. Linearly increasing serum concentrations were generated for two consecutive infusions with an anticipated slope of 0.075 μg · ml⁻¹ · min⁻¹ and a targeted concentration of 2–2.5 μg/ml. During and after the infusion, electroencephalographic data were recorded as a continuous pharmacodynamic parameter to measure the hypnotic effect. In addition, blood pressure, heart rate, pulse oximetry, clinical signs of anesthesia, and any undesirable effects were recorded. The appearance of burst suppression periods in the raw electroencephalographic wave form was used as an end point for the infusion. Arterial blood samples were drawn frequently until 720 min after the cessation of the last infusion cycle. Etnalonone serum concentrations were measured using a specific gas chromatography–mass spectrometry assay. Nonlinear regression analysis was used to relate a power spectral parameter of the electroencephalograph (median frequency) to the serum concentration using a sigmoid function model, including an effect compartment to minimize possible hysteresis. Population pharmacokinetics were analyzed using an open three-compartment model.

Results: The pharmacokinetic model parameters of etlonalone were characterized by a high total clearance (1.75 ± 0.22 l/min), small volumes of distribution (V₁ = 7.65 ± 3.40 l; V₃ = 91.6 ± 22 l), and relatively short half-lives (t₁/₂ = 1.5 ± 0.6 min; t₁/₂ = 27 ± 5 min; t₁/₂ = 181 ± 52 min). With regard to the pharmacodynamic model parameters, etlonalone proved to be a potent hypnotic agent (E₅₀ = 0.46 ± 0.09 μg/ml). The hypnotic effect coincided with a remarkable hysteresis between serum concentration and bioeffect, determined by an equilibration half-life of 8 min (kₑ = 0.087 ± 0.013 min⁻¹). All volunteers breathed spontaneously during the entire observation period and showed no clinically relevant hemodynamic changes. One volunteer experienced a convulsion during the awakening.

Conclusions: Etnalonone is a new potent steroid-type hypnotic agent with rapid elimination characteristics. Although it is short-acting, the remarkable hysteresis limits the control and might complicate administration of etlonalone if it is used as a component of a complete intravenous anesthesia regimen. Furthermore, it involves the potential disadvantage of drug accumulation and it prolongs recovery if larger-than-necessary doses are used to induce anesthesia rapidly. (Key words: Anesthetics, intravenous: etlonalone (pregnanolone). Computer-controlled infusion. Pharmacokinetic–pharmacodynamic modeling.)

LIKE several other structurally related steroids, pregnanolone (3α-hydroxy-5β-pregnan-20-one), a metabolite of progesterone, has been known for nearly 40 y to be anesthetically active without causing notable endocrinologic side effects.¹ The problem of finding a suitable solvent restricted its clinical use until 1990, when the first volunteer studies began.² Because of its low water solubility, pregnanolone was formulated as a stable oil-in-water emulsion with soybean oil and called etlonalone. After various authors³–⁶ reported largely satisfactory results using a bolus intravenous dose of etlonalone to induce anesthesia, we studied the concentration-
fect relation of this new steroid hypnotic agent using pharmacokinetic-pharmacodynamic modeling.

Materials and Methods

Twelve healthy men, ages 24–31 y (27 ± 2 y; mean ± SD), were enrolled in the study. All volunteers were within 30% of normal weight (according to the Metropolitan Life Insurance Company tables for 1980: 76 ± 5 kg; mean ± SD) and showed normal borderline electroencephalographic (EEG) results. None had documented drug allergies; known alcohol, drug, or medication abuse; or had participated in clinical studies of nonapproved drugs in the 2-week period before admission. Results of pre-study physical examinations, including blood pressure, electrocardiograms, and routine laboratory tests for all participants, were normal. The men fasted (no food, drink, or smoking) from at least 6 h before administration of the study drug to 6 h after cessation of the infusion.

The study protocol was approved by the Medical Ethics Review Committee of Freiburg, Germany, as well as by the local ethics committee and was conducted in accordance with the revised Declaration of Helsinki. All volunteers gave written informed consent.

A cannula was inserted into the radial artery of the nondominant arm and into a forearm vein of the contralateral side of each man. Hemodynamic and EEG monitoring devices were applied and after a rest of about 10 min stable baseline values of blood pressure, heart rate, oxygen saturation, and EEG were recorded. Eptanolone emulsion (1 mg/ml) was infused (Braun Perfusor Secura FT; Braun, Melsungen, Germany) via the indwelling venous cannula as two repetitive infusion cycles. The infusion rate was controlled by a computer (Toshiba 1950 C, Neuß, Germany) that was programmed to achieve venous serum concentrations of 0.0–2.5 μg/ml of unchanged eptanolone after about 20 min of infusion. The anticipated increase of the serum concentration was 0.1 μg·ml⁻¹·min⁻¹ in the first two volunteers and was then reduced to 0.075 μg·ml⁻¹·min⁻¹. The resulting infusion rate varied between 6 and 10 mg/min of eptanolone, which could only be achieved by using two parallel installed infusion pumps. Pharmacokinetic parameters obtained from bolus-dose studies were used to program the software (IVA-PUMP, version 3.2; Bonn, Germany) controlling the infusion pumps. They were the only pharmacokinetic data available at the beginning of the study. Results of recently performed bolus-dose studies also suggested that under the described conditions, a thorough observation of the induction phase might be possible. 4,6,7 Although the EEG median frequency was used as a continuous parameter for the hypnotic effect of eptanolone, clinical signs such as cessation of counting, loss of response to verbal command, and loss of the corneal reflex also were used as indicators for the course of anesthesia. The infusion was stopped when burst suppression of 1–2 s occurred in the EEG recordings. It was restarted when the volunteers were awake and fully orientated to person, place, and time. At the end of the second awakening period, monitors were removed and the volunteers were observed clinically until the next morning. During the two infusion cycles, oxygen was administered through a probe to the nose with a flow of 3 l/min. A maximum amount of 500 ml Ringer’s solution was infused to each man, and arterial Pco₂, which was analyzed from the collected blood every 6 min. To avoid interference with natural sleep, loud verbal commands were set every 2 min (“open your eyes”) when the men stopped counting until the appearance of burst suppression and from the disappearance of burst suppression until the men were fully orientated.

Collection of Blood, Drug Analysis, and Pharmacokinetic Modeling

Blood samples to determine eptanolone concentrations were collected from the indwelling arterial cannula contralateral to the infusion. The dead space of the cannula (0.1 ml) was flushed using a small amount of isotonic saline after each blood sample. Before the blood samples were collected for analysis, 1 ml blood was withdrawn and discarded. A control sample (10 ml) was drawn 3 min before the start of infusion and further samples of 5 ml each were drawn after the start of the first infusion cycle. The two infusion cycles were divided into two periods each, periods A and B and periods C and D, respectively. Period A was the first infusion, terminated by the appearance of burst suppression in the raw EEG, followed directly by period B, the first recovery period, terminated by the complete orientation of the volunteer. Period C was the second infusion, terminated again by the appearance of burst suppression patterns, followed by period D, which lasted until 12 h after the cessation of the second infusion. During periods A and C, blood samples were drawn every 3 min. During period B, blood was collected every 3 min until 30 min and then every 5 min until 60 min. The same procedure was carried out dur-
ing period D; in addition, blood samples were obtained at 90, 150, 210, 270, 390, 510, 630, and 720 min after cessation of the second infusion. The blood was collected in labeled tubes without anticoagulant and was left to clot for at least 45 min at room temperature. The serum was separated by centrifugation within 1.5 h after collection and transferred to labeled polypropylene tubes. The tubes were stored at −20°C pending analysis.

The serum samples were analyzed for unchanged etuale-nolone using a specific gas chromatographic mass spectrometric assay with selected ion monitoring (Hewlett Packard gas-chromatograph 5890, and mass selective detector 5971A). Separation was performed on a methyl silicone, 25 m × 0.2 mm capillary column with 0.11mm film thickness. Two microfilters were injected in the splitless mode for 2 min. The column oven was heated to 120°C, followed by a temperature gradient of 45°C min−1 to 280°C and the injection part to 300°C. Helium was used as the carrier gas. The mass spectrometer was operated at 70 eV ionization potential. The drug was extracted from serum with diethyl ether/pentane 1:3 (V/V). The extract was evaporated and subsequently derivatized with N,O-bis (trimethylsilyl) trifluoroacetamide was performed. 3β-hydroxy-5α-pregnane-20-one was used as an internal standard. The daily reproducibility of the method was 5 ± 1.6% (mean ± SD) with accuracy of 90–110%. The limit of sensitivity was 0.003 μg/ml. The analysis was performed in the Analytical Department, Pharmacia, Stockholm, Sweden.

The pharmacokinetic parameters were calculated (see appendix 1) and fitted using the NONMEM program, version IV, a nonlinear mixed-effects modeling algorithm developed by Beal and Sheiner.†

Electroencephalographic and Pharmacodynamic Modeling

Electroencephalographic recording began 10 min before etalanolone was administered and was continued until the early second recovery period, when the men had regained full orientation as defined previously. Electroencephalographic data were recorded using the CATTEM electrodiagnostic monitoring system (Computer-aided topographical electroencephalometry; Medisyst, Linden, Germany). Bipolar cerebral activity was monitored using an electrocap (Electro-Cap International, Eaton, OH) with the electrodes positioned according to the international 10–20 system and using Cz placement as a physical reference. The gap between the cavities of the electrodes and the tissue was bridged by an electrolytic jelly. The signals were amplified with a battery-powered amplifier close to the head, and the resulting digital code was transmitted by optical fiber to the CATTEM system. Artifact-free serial epochs of 4 s were digitized at a rate of 512 Hz (12 bit) using bandpass filters between 0.45 and 35 Hz. After smoothing the signals, the frequency analysis was performed by fast Fourier transformation. High-input impedance ensured a sufficient signal-to-noise ratio with the electrode impedances ranging from 1 to 100 kΩ. An additional display of the unprocessed raw EEG was used to check the parameters derived and to recognize the burst-suppression patterns.

For each lead, EEG analysis included the changes within the individual band power and median frequency, defined as the frequency that divides the area below the power spectrum curve into two equal parts. The individual frequency bands were set as follows: delta, 1.25–4.5 Hz; theta, 4.75–6.75 Hz; alpha1, 7.0–9.5 Hz; alpha2, 9.75–12.5 Hz; beta1, 12.75–18.5 Hz; and beta2, 18.75–35.0 Hz. To correlate the EEG changes with the serum concentrations, the values of the central lead of the dominant hemisphere (C3) were used from the 17 channels derived. Because the CATTEM system excludes the subdelta band (0.5–1.25 Hz) from the power spectral analysis, the raw EEG signal of this lead was transferred to a separate personal computer-based analysis tool. There the signal of each epoch (8 s) was converted (128 Hz, 16 bit), the power spectrum from 0.5 to 32 Hz was derived by fast Fourier transformation, and the median frequency was subsequently calculated (EEG-BASIC, version 2.4; developed by Schwinden, Bonn, Germany), thus producing more information during periods of pronounced hypnosis. The appearance of burst-suppression patterns was analyzed visually in the raw EEG, and these periods were excluded from the power spectral analysis.

In addition, the raw EEG signal was examined for amplitude artifacts and steep slopes, and a test on normal distribution was performed. The derived median frequencies were averaged to get one value per minute. The best-fit serum concentrations of the pharmacokinetic modeling were correlated to the corresponding values of the median frequency using pharmacodynamic modeling. As a basis for the modeling process, the sigmoid $E_{\text{max}}$ model was chosen to account for the nonlinearity of the concentration-effect relation (see appendix, Table 1. Results)

<table>
<thead>
<tr>
<th>Baseline</th>
<th>End of first postoperative period</th>
<th>End of second postoperative period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Values are mean (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$P &lt; 0.05$</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Statistics

The Mann–Whitney U test was used to compare central tendencies between groups for parametrically unpaired tests. The Wilcoxon signed-rank test was used to perform non-parametrically unpaired tests. The statistical analysis was performed using the StatSoft/Analyse-it software (StatSoft, Tulsa, OK).

Results

Twelve subjects were enrolled in this study. On analysis by paired comparison, no significant difference in baseline values was detected (Table 1).Subject’s data were collected after an initial bolus dose of etalanolone, followed by a constant rate infusion. A standard infusion rate of 1 mg·min−1 was administered to all volunteers. The infusion lasted for 2 h, and the concentration-time curve was obtained by sampling blood at 2-h intervals. The concentration-time data were fitted by a nonlinear mixed-effects model with the NONMEM program. The pharmacokinetic parameters were calculated using the NONMEM program, version IV, a nonlinear mixed-effects modeling algorithm developed by Beal and Sheiner.†

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Table 1. Hemodynamics during Eltanolone Infusion

<table>
<thead>
<tr>
<th></th>
<th>Systolic Pressure (mmHg)</th>
<th>Diastolic Pressure (mmHg)</th>
<th>Heart Rate (beats/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>149 ± 14</td>
<td>74 ± 10</td>
<td>68 ± 8</td>
</tr>
<tr>
<td>End of first cycle</td>
<td>119 ± 16*</td>
<td>71 ± 11</td>
<td>93 ± 11*</td>
</tr>
<tr>
<td>Start of second cycle</td>
<td>134 ± 17*</td>
<td>74 ± 10</td>
<td>83 ± 16*</td>
</tr>
<tr>
<td>End of second cycle</td>
<td>115 ± 13*</td>
<td>67 ± 10</td>
<td>88 ± 10*</td>
</tr>
<tr>
<td>Full orientation</td>
<td>138 ± 21*</td>
<td>80 ± 7</td>
<td>79 ± 16</td>
</tr>
</tbody>
</table>

Values are mean ± standard deviation of the 11 evaluated volunteers. *P < 0.05 versus baseline.

Appendix 1). Then a nonlinear regression analysis was done to identify the pharmacodynamic model parameters. In case of a time-lag (hysteresis) between the onset of the effect and the course of the serum concentration, an additional effect compartment was defined. Thus, k_{eq} was calculated within the fitting process by minimizing the hysteresis to describe the equilibration time between the central compartment (arterial blood) and the biophase or effect compartment. The course of the eltanolone concentration in the effect compartment was estimated from this procedure.

**Statistical Analysis**

The mean, SD, and SEM were used to express the central tendency of the data. The Wilcoxon matched-pairs test was performed to calculate significant changes. Probability values less than 0.05 were considered significant. The statistical evaluation was done using the program STATISTICA for Windows, release 4.5 (StatSoft, Tulsa, OK).

**Results**

Twelve young and healthy men were enrolled in the study. One man (volunteer 4) was excluded from the data analysis because of a seizure during the first awakening period, which led to his withdrawal from the study. Minor undesirable effects such as involuntary movements, excess salivation, coughing, or inspiratory stridor occurred in 100%, 25%, 25%, and 42% of the volunteers, respectively. In one man, oxygen saturation decreased to less than 90% but returned to a normal level immediately after oxygen was administered via a face mask. All participants breathed spontaneously during the entire observation period. Although the systolic blood pressure decreased significantly (P < 0.05) after the infusion of eltanolone, the diastolic and mean pressure remained largely stable. Heart rate increased significantly (P < 0.05) during both infusion cycles (table 1).

**Pharmacokinetics**

The total doses administered to the 11 volunteers during the two infusion cycles varied between 149 and 236 mg (186 ± 25 mg; mean ± SD). The serum concentration of eltanolone versus time of a representative volunteer (number 8) is shown in figure 1a together with the best-fit line and the predicted curve. Figure 2a depicts the time course of the measured concentrations for all volunteers expressed as means and SDs at the defined times of blood sampling. Table 2 summarizes the pharmacokinetic parameters using the best individ-
Table 2. Pharmacokinetic Data for Etilanolone Emulsion after Infusion and Arterial Blood Collection, Analyzed by an Open Three-compartment Model with NONMEM

<table>
<thead>
<tr>
<th>Vol. No.</th>
<th>Body Weight (kg)</th>
<th>k12 (min⁻¹)</th>
<th>k21 (min⁻¹)</th>
<th>k31 (min⁻¹)</th>
<th>Cl (L min⁻¹)</th>
<th>Vc (L)</th>
<th>Vd∞ (L)</th>
<th>t1/2 (min)</th>
<th>t1/3 (min)</th>
<th>t1/4 (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>77</td>
<td>0.24 ± 0.06</td>
<td>0.07 ± 0.007</td>
<td>0.050 ± 0.012</td>
<td>0.0050 ± 0.0006</td>
<td>1.73 ± 0.04</td>
<td>5.3 ± 0.8</td>
<td>75.6 ± 6.4</td>
<td>1.07 ± 0.20</td>
<td>16.6 ± 1.5</td>
</tr>
<tr>
<td>2</td>
<td>75</td>
<td>0.24 ± 0.05</td>
<td>0.054 ± 0.006</td>
<td>0.028 ± 0.006</td>
<td>0.0037 ± 0.0003</td>
<td>1.71 ± 0.05</td>
<td>7.6 ± 1.2</td>
<td>99.0 ± 6.2</td>
<td>1.33 ± 0.25</td>
<td>26.2 ± 2.2</td>
</tr>
<tr>
<td>3</td>
<td>69</td>
<td>0.13 ± 0.02</td>
<td>0.034 ± 0.003</td>
<td>0.039 ± 0.006</td>
<td>0.0030 ± 0.0005</td>
<td>1.72 ± 0.09</td>
<td>5.3 ± 0.6</td>
<td>94.5 ± 17.6</td>
<td>1.38 ± 0.13</td>
<td>28.1 ± 2.1</td>
</tr>
<tr>
<td>4</td>
<td>72</td>
<td>0.40 ± 0.39</td>
<td>0.059 ± 0.015</td>
<td>0.035 ± 0.002</td>
<td>0.0066 ± 0.0001</td>
<td>1.51 ± 0.08</td>
<td>3.4 ± 2.6</td>
<td>58.4 ± 6.1</td>
<td>0.75 ± 0.63</td>
<td>21.5 ± 4.4</td>
</tr>
<tr>
<td>5</td>
<td>75</td>
<td>0.08 ± 0.01</td>
<td>0.031 ± 0.005</td>
<td>0.020 ± 0.006</td>
<td>0.0044 ± 0.0005</td>
<td>1.81 ± 0.14</td>
<td>12.4 ± 2.3</td>
<td>100.8 ± 15.0</td>
<td>2.69 ± 0.31</td>
<td>34.2 ± 5.8</td>
</tr>
<tr>
<td>6</td>
<td>76</td>
<td>0.15 ± 0.02</td>
<td>0.032 ± 0.003</td>
<td>0.033 ± 0.006</td>
<td>0.0038 ± 0.0005</td>
<td>1.87 ± 0.08</td>
<td>5.7 ± 0.6</td>
<td>81.5 ± 7.8</td>
<td>1.33 ± 0.13</td>
<td>31.0 ± 3.2</td>
</tr>
<tr>
<td>7</td>
<td>72</td>
<td>0.27 ± 0.08</td>
<td>0.059 ± 0.006</td>
<td>0.050 ± 0.013</td>
<td>0.0053 ± 0.0004</td>
<td>1.49 ± 0.05</td>
<td>4.7 ± 1.1</td>
<td>70.3 ± 5.1</td>
<td>1.04 ± 0.26</td>
<td>20.9 ± 1.9</td>
</tr>
<tr>
<td>8</td>
<td>72</td>
<td>0.17 ± 0.09</td>
<td>0.038 ± 0.011</td>
<td>0.015 ± 0.006</td>
<td>0.0047 ± 0.0004</td>
<td>1.83 ± 0.11</td>
<td>12.3 ± 3.8</td>
<td>82.3 ± 9.5</td>
<td>2.59 ± 1.10</td>
<td>31.1 ± 7.0</td>
</tr>
<tr>
<td>9</td>
<td>83</td>
<td>0.17 ± 0.02</td>
<td>0.040 ± 0.003</td>
<td>0.046 ± 0.007</td>
<td>0.0047 ± 0.0004</td>
<td>1.79 ± 0.12</td>
<td>7.0 ± 1.4</td>
<td>104.7 ± 13.3</td>
<td>1.42 ± 0.17</td>
<td>27.5 ± 1.9</td>
</tr>
<tr>
<td>10</td>
<td>83</td>
<td>0.16 ± 0.03</td>
<td>0.038 ± 0.004</td>
<td>0.029 ± 0.006</td>
<td>0.0040 ± 0.0006</td>
<td>1.53 ± 0.06</td>
<td>7.6 ± 0.8</td>
<td>94.1 ± 8.0</td>
<td>1.70 ± 0.24</td>
<td>31.7 ± 3.3</td>
</tr>
<tr>
<td>11</td>
<td>84</td>
<td>0.19 ± 0.10</td>
<td>0.063 ± 0.008</td>
<td>0.032 ± 0.014</td>
<td>0.0048 ± 0.0003</td>
<td>2.29 ± 0.07</td>
<td>13.0 ± 4.7</td>
<td>146.3 ± 8.2</td>
<td>1.63 ± 0.69</td>
<td>26.2 ± 2.7</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>76 ± 5</td>
<td>0.19 ± 0.09</td>
<td>0.046 ± 0.014</td>
<td>0.036 ± 0.013</td>
<td>0.0045 ± 0.0008</td>
<td>1.75 ± 0.22</td>
<td>7.7 ± 3.4</td>
<td>91.6 ± 22.0</td>
<td>1.54 ± 0.58</td>
<td>26.8 ± 5.1</td>
</tr>
</tbody>
</table>

Values are estimates ± standard error of the individual fits and means ± standard deviations of the 11 evaluated volunteers.
Table 3. Pharmacodynamic Modeling Data for Eltanolone Emulsion

<table>
<thead>
<tr>
<th>Volunteer No.</th>
<th>E0 (Hz)</th>
<th>Emax (Hz)</th>
<th>Cp50 (µg·mL⁻¹)</th>
<th>γ</th>
<th>ke0 (min⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9.1 ± 0.3</td>
<td>8.0 ± 0.3</td>
<td>0.55 ± 0.02</td>
<td>8.0 ± 1.7</td>
<td>0.062 ± 0.004</td>
</tr>
<tr>
<td>2</td>
<td>8.0 ± 0.2</td>
<td>7.1 ± 0.2</td>
<td>0.31 ± 0.01</td>
<td>3.1 ± 0.2</td>
<td>0.079 ± 0.002</td>
</tr>
<tr>
<td>3</td>
<td>9.3 ± 0.2</td>
<td>8.3 ± 0.3</td>
<td>0.45 ± 0.04</td>
<td>6.8 ± 1.9</td>
<td>0.096 ± 0.011</td>
</tr>
<tr>
<td>4</td>
<td>8.3 ± 0.3</td>
<td>7.4 ± 0.3</td>
<td>0.57 ± 0.01</td>
<td>7.0 ± 1.0</td>
<td>0.080 ± 0.002</td>
</tr>
<tr>
<td>5</td>
<td>8.1 ± 0.1</td>
<td>7.5 ± 0.2</td>
<td>0.57 ± 0.02</td>
<td>4.4 ± 0.5</td>
<td>0.088 ± 0.005</td>
</tr>
<tr>
<td>6</td>
<td>8.3 ± 0.1</td>
<td>7.3 ± 0.1</td>
<td>0.44 ± 0.01</td>
<td>6.9 ± 0.6</td>
<td>0.085 ± 0.003</td>
</tr>
<tr>
<td>7</td>
<td>9.0 ± 0.2</td>
<td>8.2 ± 0.2</td>
<td>0.53 ± 0.01</td>
<td>5.7 ± 0.7</td>
<td>0.078 ± 0.002</td>
</tr>
<tr>
<td>8</td>
<td>9.1 ± 0.1</td>
<td>7.1 ± 0.1</td>
<td>0.38 ± 0.01</td>
<td>4.6 ± 0.4</td>
<td>0.109 ± 0.003</td>
</tr>
<tr>
<td>9</td>
<td>9.0 ± 0.1</td>
<td>9.0 ± 0.1</td>
<td>0.39 ± 0.01</td>
<td>6.7 ± 0.5</td>
<td>0.091 ± 0.003</td>
</tr>
<tr>
<td>10</td>
<td>8.8 ± 0.2</td>
<td>8.1 ± 0.2</td>
<td>0.43 ± 0.01</td>
<td>6.3 ± 0.8</td>
<td>0.104 ± 0.005</td>
</tr>
<tr>
<td>11</td>
<td>8.7 ± 0.2</td>
<td>7.5 ± 0.2</td>
<td>0.45 ± 0.01</td>
<td>9.2 ± 1.1</td>
<td>0.086 ± 0.001</td>
</tr>
<tr>
<td>12</td>
<td>8.7 ± 0.6</td>
<td>7.8 ± 0.6</td>
<td>0.46 ± 0.09</td>
<td>6.2 ± 1.7</td>
<td>0.067 ± 0.013</td>
</tr>
</tbody>
</table>

Values are estimates ± standard error of the individual fits and mean ± standard deviation of the 11 evaluated volunteers.

E0 = EEG median frequency when the patient is awake (baseline); Emax = maximal decrease of the EEG median frequency; Cp50 = drug concentration necessary to achieve 50% of the maximal effect; γ = power parameter describing the steepness of the sigmoid curve; ke0 = rate constant of drug removal from the effect compartment.

die (number 8) are shown in figure 1b. The time course for all volunteers is plotted in figure 2b as means and SDs at the times of blood sampling. Median frequency decreased significantly from the ninth minute after the start of the first infusion (P < 0.01) until the 24th minute of the first recovery period (P < 0.05). The maximal decrease during the first cycle was achieved 5 min after cessation of the infusion, with 0.84 ± 0.09 Hz (mean ± SD; P < 0.001). In the second cycle, median frequency was significantly less than the baseline from the sixth minute after the start of the infusion (P < 0.01) until the 30th min of the second recovery period (P < 0.05). Using the appearance of burst-suppression patterns as an end point, the infusion time lasted 19.3 ± 2.9 min (mean ± SD) in the first loop and 14.8 ± 2.5 min in the second loop. Full orientation was regained 35 ± 6 min after the cessation of the infusion in the first cycle and 38 ± 7 min in the second cycle, respectively.

Table 3 summarizes the pharmacodynamic modeling parameters of the individual volunteers. The Cp50 was 0.46 ± 0.09 µg/ml. Furthermore, we found a hysteresis between arterial serum concentration and response, with an equilibrium half-life of about 8 min (kneq = 0.087 ± 0.013 min⁻¹) and a relatively steep concentration-response relation (γ = 6.2 ± 1.7). Using the EEG median frequency and the arterial serum concentrations, the concentration-versus-effect plot of figure 3a of a representative volunteer (number 8) describes a wide hysteresis loop. As shown in figure 3b using the estimated effect compartment concentrations of eltanolone, a consistent sigmoid relation between concentra-

tion and effect was derived. The relation between the concentration in the effect compartment and the EEG median frequency is plotted for each volunteer in figure 4, illustrating the interindividual variability in pharmacodynamics. With regard to clinical signs such as falling asleep (cessation of counting) or loss of response to loud verbal commands, sufficient conformity was found (fig. 5). Only small differences remain in the concentrations for the loss and the reappearance of clinical signs, respectively.

Discussion

Eltanolone emulsion is a new steroid intravenous anesthetic that has already been found to be a potent hypnotic in previously published dose-finding studies by judging clinical criteria for successful induction of anesthesia. van Hemelrijk and colleagues examined the relative potency of eltanolone using logistic regression analysis. They found it to be 3.2 times more potent than propofol and six times more potent than thiopental. In the present study, in which we applied a pharmacokinetic-pharmacodynamic modeling procedure with a sigmoid Emax function after computer-controlled infusion, eltanolone also proved to be a potent hypnotic. Its Cp50 of 0.46 µg/ml indicates a hypnotic potency comparable to that of etomidate (0.32 µg/ml) and about four times greater than that of propofol (2.5 µg/ml).

The pharmacokinetic data obtained in this study
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Fig. 3. (a) Arterial serum concentrations of a representative volunteer (number 8) plotted against the electroencephalographic median frequency. The arrows indicate the increase and decrease of the serum concentration. The wide hysteresis loop illustrates the effect hysteresis of etalolone. (b) Using the estimated effect compartment concentrations of the same volunteer, an analogous plot yields a sigmoid relation between concentration and effect.

showed the rapid elimination characteristics of etalolone. The total clearance of 25 ml · min⁻¹ · kg⁻¹ is nearly in the same range as that of propofol at 28 ml · min⁻¹ · kg⁻¹.¹⁰ As was expected based on comparable studies with other hypnotics, the central volume of distribution after infusion and arterial blood sampling was found to be significantly (P < 0.05) smaller (about four times) than that reported after bolus injection and venous blood collection (0.11 ± 0.01 L/kg instead of 0.42 ± 0.23 L/kg). This explains the systematic underestimation of serum concentrations during induction by the computer simulation, which applied the bolus data set. With regard to the best-fit data of the NONMEM model-dependent pharmacokinetic analysis, it is evident that the predicted peak values regularly remain less than the measured serum concentrations. This might be due to nonlinear kinetic behavior at higher concentrations with a decreasing total clearance, which is, however, not supported by the results of previous bolus-dose studies. Furthermore, it might show a fundamental problem of traditional pharmacokinetic models, making the assumption that each compartment is continuous and that the drug administered mixes instantaneously.¹²

In reality, especially at high infusion rates, compartments might be discontinuous and separated by circulation delays.¹³ Conventional compartment models do not incorporate circulation delays, and the applied three-compartment model failed to describe exactly the measured peak concentrations of etalolone in this study.

With respect to the pharmacodynamic parameters of etalolone, this study revealed a high hypnotic efficacy. It was, however, accompanied by a hysteresis (8 min equilibration half-life) that clearly exceeds the values of other hypnotics, such as thiopental (1.5 min) and propofol (3 min). Enitidate and ketamine do not show any measurable hysteresis. Because the physiological properties of etalolone do not provide obvious reasons for this hysteresis, we speculated that a delayed diffusion into the brain or protracted receptor binding causes the time lag between concentration and the corresponding effect.

Another possibility was discovered by Wang and colleagues, who found that an albumin solution of 5α-pregnanolone was more potent in inducing anesthesia than an intralipid emulsion of the same compound.

Thus we can confirm that the use of lipid emulsions was possible with the 5α-pregnanolone solution, and 50 s after beginning the infusion the volunteers reported only minimal awareness, probably due to the simultaneous brain equilibration of the delay time. The delay after bolus injection is increased compared to a delayed delayed effect related to a delay time.

Therefore, another approach is to calculate the mean concentration for each individual computer-generated model to achieve satisfactory results in brain and measured probative parameters. Dynamic plasma concentration after bolus injection is needed to validate the model, and the model should be validated with different groups of patients, e.g., older patients. The model should be compared to the model for plasma concentration and recovery time. The model should be validated with different groups of patients, e.g., older patients.
PHARMACOKINETIC-DYNAMIC MODELING OF ELTANOLONE

Fig. 5. Relation between clinical signs for the course of anesthesia, effect compartment concentrations, and the effect (percentage). The clinical signs disappeared at only slightly higher concentrations than they reappeared.

Thus we could conclude that the release of steroids out of lipid emulsions might be delayed. Nevertheless, it was possible to achieve induction times between 40 and 50 s after administering a bolus dose of 0.75 mg/kg (about double the median effective dose) of eltanolone emulsion in recently performed studies in patients, with only minor hemodynamic side effects.1,7 This is probably due to the rapid initial decline of the serum concentrations after bolus injection, caused by redistribution, that leads to a quick adaptation of the peak serum concentration in the effect compartment, despite the long equilibration half-life. Thus, if the dose is large enough, the delay of induction will be of minor clinical relevance after bolus injections. However, during total intravenous anesthesia, if the effect of eltanolone must be increased or decreased rapidly, hysteresis will at first lead to a delayed response, and the steep concentration-effect relation (γ = 6.2) will cause a sudden reaction. Therefore, control of the anesthetic effect is limited.

Another aspect will be the danger of overdose unless the meaning of the small k₄₅ is well understood or computer-controlled infusion devices programmed to achieve specific drug concentrations at the effector site in brain are used. The bolus-dose studies in the patients noted previously1,7 confirm the relatively small hemodynamic side effects up to doses of 0.8 mg/kg body weight of eltanolone. Myint and colleagues12 suggested that the induction dose in elderly patients (60 y or older) should not exceed 0.6 mg/kg, and moreover they found indications for a much slower pharmacodynamic response compared with propofol and thiopental. Kallela and coworkers13 registered significantly longer recovery times after 0.8 mg/kg eltanolone was administered compared with 2 mg/kg propofol.

As a representative monoparametric value that summarizes the complex changes within the entire electrical cortex activity, EEG median frequency again proved to be a practical and reliable continuous measure for the central effect of a single hypnotic agent.4,19,20 Changes in the EEG power spectrum and median frequency, found after infusion of eltanolone, correlated well with the clinical course of anesthesia and were comparable to those described after the administration of other hypnotics such as thiopental, etomidate, and propofol.4,19,22 The pharmacodynamic end point used in this study was the appearance of burst suppression of the raw EEG wave form. Calculation of the median frequency, however, becomes unstable as the EEG bears the discontinuous phenomenon of burst suppression. To incorporate EEG activity at high serum concentrations in the pharmacodynamic modeling procedure, frequencies as low as 0.5 Hz had to be considered. Therefore, it was necessary to extend the CATEEM system by the capability offered through an additional analysis tool (EEG-BASIC). The comparison between the course of median frequency and clinical signs revealed good conformity. The small discrepancies remaining are probably caused by time-recording inaccuracies for the clinical signs, particularly with respect to the steepness of the concentration-effect relation.

Although eltanolone is thought to have anticonvulsive properties by acting at the gamma-aminobutyric acid receptor,23,24 one volunteer experienced a seizure after the first infusion during awakening. This coincided with seizure activity in his raw EEG recordings showing polyspike waves. Medical history and results of all prestudy examinations, including his baseline EEG, were normal, as were those of the poststudy screening on the day.
after infusion. Seizure-like movements have been reported after all known hypnotics, but in nonepileptic patients mostly without EEG seizure activity.\textsuperscript{1,20} This incidence would make it necessary to examine systematically under which circumstances etomidate could develop proconvulsant effects, because this might be a severe contraindication of this drug.

At this stage of evaluation, etomidate was shown to be a potent hypnotic agent with rapid elimination characteristics and relatively minor cardiovascular and respiratory side effects in healthy volunteers and patients. Induction characteristics were satisfactory after bolus injection, and the most frequent undesirable effects reported were involuntary movements and myoclonus. The equilibration half-time of 8 min between central compartment and effect compartment is a clear disadvantage compared with other hypnotics in that control of the compound is reduced. Furthermore, it involves the potential disadvantage of drug accumulation and prolongation of recovery if larger-than-necessary doses of etomidate are used to induce anesthesia rapidly or to control rapidly the sudden responses to noxious stimulation during an operation. These findings, together with possible proconvulsant properties and increased incidence of urticaria, have led to the termination of the etomidate project.

References

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Appendix 1: Pharmacokinetic and Pharmacodynamic Formulas

The serum concentration $c(t)$ was calculated by convolution using the following formulas:

$$
c(t) = \int_0^t g(t-t') \cdot r(t') \, dt'$$

$$
g(t) = A_1 \cdot e^{-\lambda_1 t} + A_2 \cdot e^{-\lambda_2 t} + A_3 \cdot e^{-\lambda_3 t}$$

where $g(t)$ describes the concentration after a bolus dose and $r(t)$ is the infusion rate applied. The macro constants $A_1$, $A_2$, $A_3$, $\lambda_1$, $\lambda_2$, and $\lambda_3$ were computed from the pharmacokinetic parameters $k_{12}$, $k_{21}$, $k_{13}$, $k_{31}$, $Cl$, and $V_c$.

The pharmacodynamic effect was described by the modified Hill equation:

$$
E(t) = E_0 - E_{\text{max}} \frac{c(t)^\gamma}{c(t)^\gamma + c_{\text{iso}}^\gamma}
$$

where $E(t)$ is the EEG median frequency measured at time $t$, $E_0$ is the baseline median frequency, $E_{\text{max}}$ is the maximum effect, $c_{\text{iso}}$ is the half-maximum effect concentration, and $\gamma$ defines the steepness of the concentration effect curve. The concentration in the effect compartment $c_i(t)$ is given by

$$
c_i(t) = k_{3i} \cdot \int_0^t e^{-k_{3i} t'} \cdot c(t') \, dt'$$

where $c_i(t)$ is the serum concentration and $k_{3i}$ is the elimination rate out of the effect compartment.