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Concentration-Effect Relationships of Eltanolone Given as a Bolus Dose or Constant Rate Intravenous Infusion to Healthy Male Volunteers

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Background: **The primary purpose of this study was to evaluate concentration-effect relationships of the new steroid anesthetic eltanolone during recovery from a bolus dose and constant rate intravenous infusion in healthy male volunteers.**

Methods: **Ten subjects received a bolus dose of 0.75 mg/kg eltanolone over 20 s. A 2-h constant rate intravenous infusion of eltanolone was given to five subjects at a rate of 2 $mg \cdot kg^{-1} \cdot h^{-1}$ and to another five subjects at a rate of 3.5 $mg \cdot kg^{-1} \cdot h^{-1}$. Recovery performance was assessed as the time required to reach different end-points and by means of three different psychomotor tests.**

Results: **A low interindividual variability was found in the serum concentration of eltanolone at the pharmacodynamic end-points during recovery. The Cp_{50} value for "eye opening" was 382 μg/l (95% confidence interval, 285–489) after a bolus dose corresponding to a median time of 16 min (range 8–25). After eltanolone infusion, the Cp_{50} value for "eye opening" was 507 μg/l (95% confidence interval, 425–605) and the corresponding median time was 21 min (range 8–25) in the low-dose group and 49 min (range 31–66) in the high-dose group. The Cp_{50} values at the same effect end-points in the bolus group were less than those in the infusion groups, probably because of insufficient equilibration time between serum and the effect compartment.**

Conclusions: **Recovery characteristics of eltanolone were predictable because of a relatively low interindividual variability in serum concentrations but with a slow blood:effect compartment equilibration. (Key words: Anesthetics, intravenous: eltanolone; pregnanolone. Pharmacodynamics: eltanolone; pregnanolone.)**

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THE anesthetic effect of steroid hormones was described by Seyle as early as 1941.[1] Progesterone, pregnenolone, and related 5-alpha-pregnane compounds were described as having anesthetic effects in rats. Another steroid molecule, 3α-hydroxy-5β-pregnan-20-one, was shown to have anesthetic properties in mice without significant endocrine effects.[2] Later, pregnanolone, a metabolite of progesterone, was shown to have significant anesthetic potency in several animal species.[3] All of these compounds are poorly soluble in water. The use of pregnanolone (eltanolone) as an anesthetic agent in humans has now been made possible by the formulation of a lipid emulsion preparation. Pharmacokinetic and pharmacodynamic studies with the new eltanolone emulsion preparation have been performed in volunteers.[4,5]

Eltanolone is a highly cleared drug (1.23–1.54 $l \cdot kg^{-1} \cdot h^{-1}$) with a large volume of distribution at steady state (1.7–1.9 l/kg). The latter parameter indicates an extensive distribution outside of plasma.[5]

However, knowledge of the pharmacodynamic effects of eltanolone during emergence from anesthesia is still very limited. This scarcity of data also includes a lack of information about concentration-effect relationships of eltanolone as well as Cp_{50} values at different pharmacodynamic effect end-points during recovery.

The primary objective of this study was to evaluate the pharmacodynamic responses during recovery from eltanolone anesthesia and their relationship to the corresponding serum concentrations.

Subjects and Methods

Healthy Volunteers

The study was divided into two parts, with ten healthy male volunteers participating in each. Seven of the subjects participated in both parts of the study. There

Table 1. Demographics of the Subjects

	Age (yr)	Body Weight (kg)	Height (cm)
Bolus injection (n = 10)			
Mean	30.0	77.5	181.3
SD	4.6	9.7	4.4
Low infusion rate (n = 5)			
Mean	28.6	76.8	182.2
SD	4.7	6.5	4.4
High infusion rate (n = 5)			
Mean	26.2	72.4	182.0
SD	4.6	3.8	5.1

was an interval of 3 months between studies. All subjects were men aged between 18 and 45 yr, and all were nonsmokers. Their state of health was good as based on a prestudy physical examination including blood pressure and ECG, and a prestudy laboratory screening and no history of previous anesthetic complications, allergy, or abuse of alcohol or drugs was found. None was receiving concurrent drug therapy. Demographic data for the subjects are summarized in table 1. The study was approved by the Ethics Committee of the Medical Faculty at Uppsala University and informed consent was obtained from all participants.

Eltanolone Dose and Anesthetic Monitoring

In the first part of the study, ten subjects were given an intravenous bolus dose of 0.75 mg/kg eltanolone emulsion over 20 s (4 mg/ml; Pharmacia Hospital Care, Stockholm, Sweden) through an intravenous catheter in an antecubital vein. The dose chosen was based on previous experience in studies done on volunteers and patients.[5,6] In the second part of the study ten subjects were given a constant rate intravenous infusion of eltanolone emulsion (4 mg/ml) during 2 h (Terufusion STC 521, Tokyo, Japan). In the first five subjects, the infusion rate was 2 $mg \cdot kg^{-1} \cdot h^{-1}$ and in the remaining five subjects, 3.5 $mg \cdot kg^{-1} \cdot h^{-1}$. The infusion regimen was based on pharmacokinetic data from the bolus dose group. The smaller dose was chosen as a dose that could produce a serum concentration of 1100 $\mu g/l$, above the concentration at which anesthesia could be induced ($\approx$600–700 $\mu g/l$), and the larger dose aimed at a concentration of 2,000 $\mu g/l$. The subjects were allowed nothing by mouth from midnight and the morning of the study they were given an infusion of a buffered glucose-electrolyte solution (Glucos Pharmacia 50 mg/ml buffrad, Pharmacia, Stockholm, Sweden) during about 4 h and at at rate of 1 or 2 $ml \cdot kg^{-1} \cdot h^{-1}$. All subjects were breathing spontaneously during anesthesia with supplemental oxygen, 2 l/min, *via* the nasal route and were monitored continuously with pulse oximetry (Novametrix 515 A, Novametrix Medical Systems Inc, Wallingford, CT), electrocardiogram (Diascope DS 521, S&W Medicoteknik, Albertslund, Denmark), and noninvasive blood pressure measurements (Sirecust 888, Siemens, Germany). Venous blood gases also were analyzed before and at the end of infusion to detect possible carbon dioxide retention caused by hypoventilation.

The criterion for induction of anesthesia was the loss of verbal contact or loss of response to verbal stimuli measured from the start of injection or infusion of eltanolone.

Effect Measurements

After infusion of eltanolone, hypnotic effect was assessed by responses to verbal and tactile stimuli, which were recorded at 60, 90, and 120 min after start of infusion. A modified RLS-85 scoring scale, presented in table 2, was used.[7]

Three different early recovery end-points were recorded as the time from start of injection or termination of infusion until the subject opened his eyes on command, was oriented to time, place, and person, and as the time the subject was able to sit up in bed unsupported for 10 s. Early recovery was measured at 1-min intervals until the subject reached each end-point.

Two different intermediate recovery end-points also were recorded as the time until the subject tolerated oral fluids and was able to walk 10 m without assistance. The measurements during intermediate recovery were performed at 30-min intervals up to 120 min or until the subject reached each end-point.

Three different psychomotor tests also were used as a measure of recovery. The Maddox wing device[8] was used to measure the balance of extraocular muscles:

Table 2. Modified Reaction Level Score for Hypnotic Effect

Score	RLS 85
1	Awake and responsive
2	Drowsy but easily responsive to verbal stimuli
3	Very drowsy but rousable and responsive to tactile stimuli
4	Unconscious, localizes but does not ward off tactile stimuli
5	Unconscious and withdrawal movement on tactile stimuli
6	Unconscious and flexing movement on tactile stimuli
7	Unconscious and extension movement on tactile stimuli
8	Unconscious and unresponsive to verbal or tactile stimuli

the amount of esophoria or exophoria was expressed in prism diopters. The digit symbol substitution test[9] was used to measure changes in sensory processing performance and ability to concentrate. The critical flicker fusion threshold[10,11] was used as an objective measurement of alertness (Critical Flicker Fusion Tester, Leeds Psychomotor Services, Acomb, York, England). Critical flicker fusion threshold is an index of central nervous system arousal and of the subject's ability to integrate discrete units of sensory data. The frequency of the flicker was increased from 10 Hz to 50 Hz and thereafter decreased in a similar manner, and the point at which the subject could detect either flicker or fusion was recorded. Psychomotor tests were done at baseline (before induction) and at 30, 60, 90, 120, 180, 240, 300, 420, and 540 min after start of injection of bolus or end of infusion. Measurements were also done approximately 24 h after start of infusion. Observed secondary effects and adverse events also were recorded.

Blood Sampling and Drug Analysis

In the bolus group, venous blood samples were collected before drug administration and at 1, 3, 5, 7.5, 10, 15, 30, 45 min and thereafter at 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12 h after start of injection. In the infusion group, venous blood samples were collected before drug administration and at 3, 6, 9, 15, 30, 45, 60, 90, and 120 min after start of infusion. Further samples were taken at 2, 4, 6, 8, 10, 20, 40, 60 min and 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, and 18 h after the end of infusion. All blood samples were drawn from an intravenous catheter inserted in an antecubital vein in the arm contralateral to the site of drug administration. Before the withdrawal of any blood sample, 1 ml fluid was withdrawn and discarded. The blood samples were collected in tubes (Venoject) without anticoagulant and were left to clot for at least 45 min before serum was separated by centrifugation (3,000 rpm for 10 min). Serum was then transferred by means of a glass pipette to polypropylene tubes and stored at −20°C pending analysis. The analytical method for assay of serum concentrations of eltanolone was based on gas chromotography-mass spectrometry (Hewlett Packard gas-chromotograph 5890 and mass selective detector 5971A; Hewlett Packard, Oregon). Separation was performed on a methyl silicone capillary column, 25 m × 0.2 mm, with 0.11 mm film thickness. The injector temperature was 300°C. Injection of 2 μl was performed in the splitless mode for 2 min. The column temperature was then increased from 120°C to 280°C by 45°C/min^{-1} and held at the final temperature for 7 min. Helium was used as carrier gas. The mass spectrometer was operated at 70 eV ionization potential. The ions m/z 300 and 375 were followed. The method comprised extraction from serum with diethyl ether/pentane 1:3. The extract was evaporated and subsequently a derivatization was performed with N, O-bis (trimethyl-silyl) trifluoroacetamide. 3β-hydroxy-5α-pregnan-20-one was used as internal standard. The between-days reproducibility of the method was around 5% with an accuracy of 90–100%. The limit of quantification was 1 μg/l.

Blood samples for laboratory screening also were taken immediately before drug administration and 24 h after administration.

Calculations and Statistical Analysis

Serum concentrations of eltanolone obtained for each subject were plotted against time. This plot was used to make a linear interpolation of the eltanolone serum concentration at times that did not coincide with sampling times. The serum concentration of eltanolone was related to the time when each subject reached the effect end-points during early and intermediate recovery. The Cp_{50} values for all effect end-points during early recovery and for one effect end-point during intermediate recovery were estimated according to Wilcoxon signed rank method.[12] The Bonferroni-Holms procedure for multiple comparisons also were used to calculate 95% confidence limits and *P* values.[13] Cp_{50} values represent the serum concentration corresponding to an effect in 50% of the subjects. Coefficients of variation were also calculated for these end-point. Effect compartments concentrations were simulated using the mean elimination rate constant data (K_{eo} = 0.1 min^{-1}) from a study on pharmacodynamic modeling of eltanolone's electroencephalogram (EEG) drug effects by Schüttler *et al.*[14] Psychomotor performance between groups was compared using the Mann-Whitney *U* test. $P < 0.05$ was considered statistically significant.

Mean values and standard deviations were calculated using standard equations. All data are presented as mean ± SD and/or median and minimum and maximum.

Results

Induction of Sleep

There were no differences in demographic data between the groups (table 1). The median time to loss

of verbal contact was 37 seconds (range, 34–45) after a bolus dose. In the subjects given an eltanolone infusion at the low dose, the median time to loss of verbal contact was 19 min (range: 12–20) as compared to 9 min (range, 7–13) after the high dose. Induction was smooth in all subjects and a sense of well-being was reported by those in the infusion group. No excitatory phenomena or pain on injection were observed in any of the subjects.

The cardiovascular responses in the bolus group are shown in figures 1 and 2. Mean arterial pressure decreased with a maximum reduction of 10% at 4 min after start of injection. Mean arterial pressure had returned to baseline within 20 min. Heart rate increased after induction with a maximum increase of 21% 1 min after induction and had returned to baseline within 30 min. In the two infusion groups, mean arterial pressure decreased with a maximum reduction of 7% at 15 min after start of infusion and returned to baseline within 30 min and thereafter remained stable throughout the infusion period. Heart rate slowly increased after starting the infusion with a maximum increase of 24% after 60 min. Heart rate returned to baseline within 60 min after end of infusion. There were no indications of hypoventilation in the infusion group because the ventilatory pattern was normal and no changes could be seen in the pulse oximetry monitoring. There were no statistically significant changes in the venous partial pressure of carbon dioxide between preinfusion and before the end of infusion: 6.79 ± 0.52 kPa (51 ± 3.9 mmHg) and 7.22 ± 0.65 kPa (54 ± 4.9 mmHg; mean ± SD), respectively ($P > 0.05$, Wilcoxon matched pairs test).

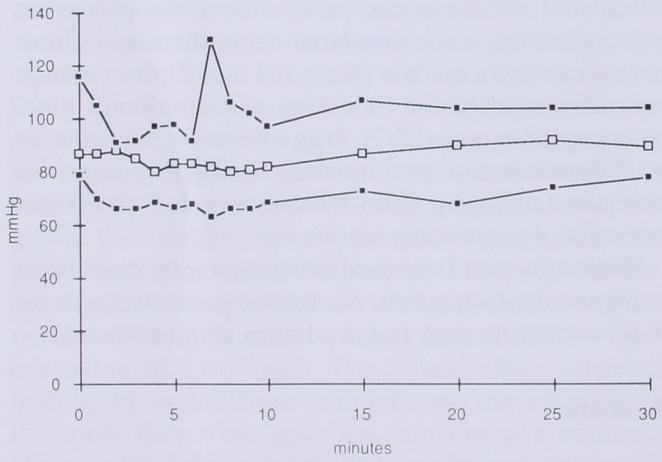

Fig. 1. Median and range of individual mean arterial blood pressures during the first 30 min after a bolus dose of 0.75 mg/kg eltanolone (median □ and min-max ■) n = 10.

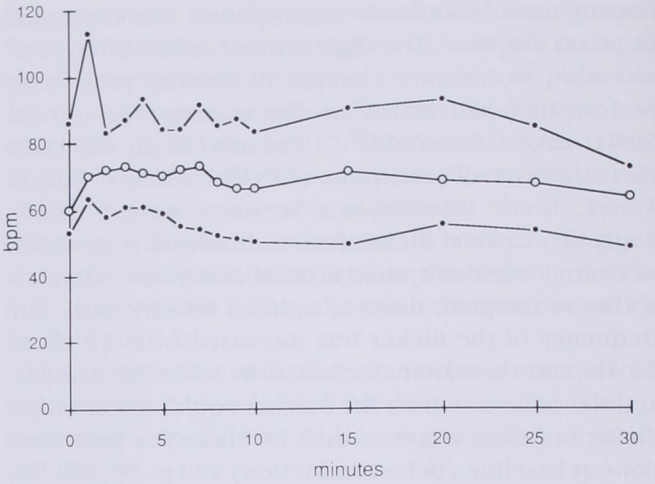

Fig. 2. Median and range of individual heart rates during the first 30 min after a bolus dose of 0.75 mg/kg eltanolone (median □ and min-max ■) n = 10.

Anesthesia

Assessment of hypnotic effect according to the modified RLS-85 scoring scale (table 2) showed that at 60 min, four subjects given the low dose infusion were unconscious and had withdrawal movements to tactile stimuli (score = 5). One subject was unconscious but could localize tactile stimuli (score = 4). The corresponding mean serum concentration of eltanolone at this time was 1121 ± 158 μg/l (mean ± SD). At 90 and 120 min, all subjects were unconscious with withdrawal movements to tactile stimuli (score = 5), and the corresponding serum concentrations of eltanolone were 1,172 ± 183 μg/l and 1263 ± 61 μg/l (mean ± SD), respectively. In the group receiving the high infusion dose, one subject was unresponsive (score = 8) and the rest had scores = 5 at all three observation times. The corresponding serum concentrations of eltanolone were 2,204 ± 265 μg/l, 2,268 ± 97 μg/l and 2,671 ± 268 μg/l (mean ± SD) for the 60-, 90-, and 120-min assessments, respectively.

Recovery

Recovery times and Cp_{50} concentrations for early and intermediate recovery are presented in tables 3 and 4. Differences in concentrations at the same recovery endpoints were observed between the bolus and the infusion groups. They were most pronounced at the end-

Table 3. Times after Bolus Dose or Postinfusion for Early and Intermediate Recovery End Points in All Groups

	Loss of Verbal Contact	Eye Opening (min)	Orientation (min)	Able to Sit 10 s (min)	Able to Walk 10 m (min)
Bolus injection (s)					
Mean	37	15	20	23	42
SD	3	4	5	6	10
Median	37	16	19	22	39
Range	34–45	8–25	11–31	14–37	35–68
Low infusion rate (min)					
Mean	17	22	35	36	63
SD	3	7	7	10	17
Median	19	21	38	40	70
Range	12–20	12–32	23–42	19–46	37–85
High infusion rate (min)					
Mean	10	50	65	67	94
SD	2	13	16	16	12
Median	9	49	64	66	100
Range	7–13	31–66	46–94	47–95	70–103

points for "opening eyes on command" and "able to walk 10 m without assistance." However, these differences were not statistically significant using Bonferroni-Holms procedure for multiple comparisons (table 4). At all end-points, relatively low interindividual variation in eltanolone concentrations were found in both groups (table 4).

The simulated effect compartment concentrations (figs. 3 and 4) and serum concentrations at the mean time points for open eyes and orientation also were compared in all groups. The differences between the bolus and infusion group were only 4% or 5% in effect compartment concentrations as compared to the 30–40% difference in serum concentrations due to the hysteresis between drug serum concentration and drug effect compartment concentration.

Psychomotor Performance

The median psychomotor performance level (critical flicker fusion threshold and digit symbol substitution test) reached a stable level above 90% of baseline values 60–90 min after end of drug administration in both groups. No differences were seen in the critical flicker fusion threshold test between anyone of the groups. All were back to 100% of baseline by 7 h in the bolus group and by 5 h in the infusion group, except for one subject given the low dose who had reached 94% of his baseline performance level. In the digit symbol substitution test, no differences were seen between the infusion groups from 3 h and onward. All subjects in the bolus group were back to 100% of baseline by 5 h and in the infusion group after 4 h (low dose) and 7 h (high dose; figs. 5 and 6). A greater learning effect were observed in the bolus group, leading to a significant difference compared to the infusion groups at 3, 4, and 5 h. Finally, in the Maddox wing test, no significant differences were seen between the infusion groups and only at 1 and 1.5 h between the bolus and infusion groups. All but one subject had returned to his own baseline performance by 7 h in the bolus group

Table 4. Cp_{50} Values and Coefficients of Variation (CV) at Different Effect End Points

End Point	Bolus Injection	CV (%)	IV Infusion	CV (%)	*P* Value*
Eye opening	382 (285–489)	37	507 (425–605)	25	0.037
Orientation	346 (264–428)	34	440 (361–521)	25	0.130
Able to sit	329 (238–415)	36	421 (348–509)	25	0.096
Able to walk	224 (171–278)	32	305 (265–345)	18	0.021

Cp_{50} values (Wilcoxon signed rank method) based on the serum concentrations ($\mu g \cdot L^{-1}$) interpolated from the measured eltanolone concentration time curve. The 95% confidence interval and the *P* value obtained from the Bonferroni-Holms procedure for multiple comparions are also presented.

* *P* values are uncorrected for the multiplicity.

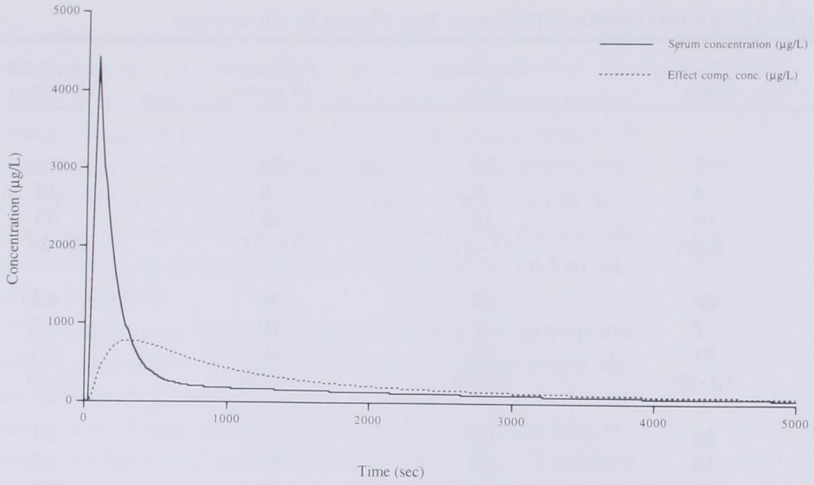

Fig. 3. Simulation of serum-and effect compartment concentrations of eltanolone after a bolus dose (0.75 mg/kg).

and in the infusion group by 5 h (low dose) and 7 h (high dose).

Adverse Events

The adverse events observed in this study are summarized in table 5. The most frequently observed adverse event was minor involuntary movements. No nausea and vomiting or venous sequelae were reported during the 24-h observation period.

One of the subjects in the bolus group experienced airway obstruction during emergence from anesthesia owing to rigidity and had a short period of apnea, coughing, and a decay in oxygen saturation that was easily resolved by airway support consisting of jaw elevation. He did not require airway insertion.

One serious adverse event was observed in one of the subjects given the high infusion dose of eltanolone. Four hours postinfusion, when the subject was fully ambulatory, he suddenly had generalized seizures that resolved spontaneously within 2 min without the need for drug intervention. Only airway support and oxygen supplementation were required for about 5–10 min. The subject experienced post-ictal tiredness, amnesia, headache, nausea, and vomiting for several hours. He was fully recovered the next day but was excluded from evaluation with the psychomotor tests. No significant clinical changes could be seen in the prestudy and poststudy laboratory screening. All subjects felt well at the 2-week poststudy follow-up.

Discussion

A relatively low interindividual variability in measured serum concentrations of eltanolone at the ob-

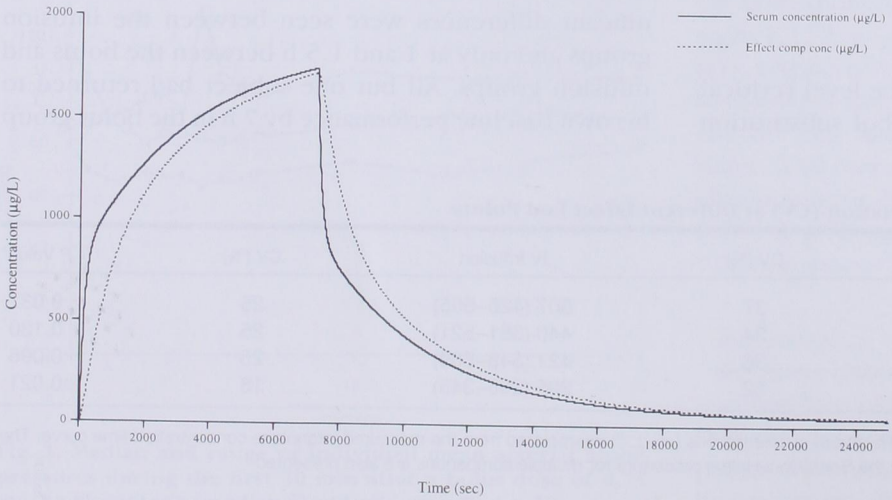

Fig. 4. Simulation of serum and effect compartment concentrations of eltanolone after a 2-h high dose infusion (3.5 $mg \cdot kg^{-1} \cdot h^{-1}$).

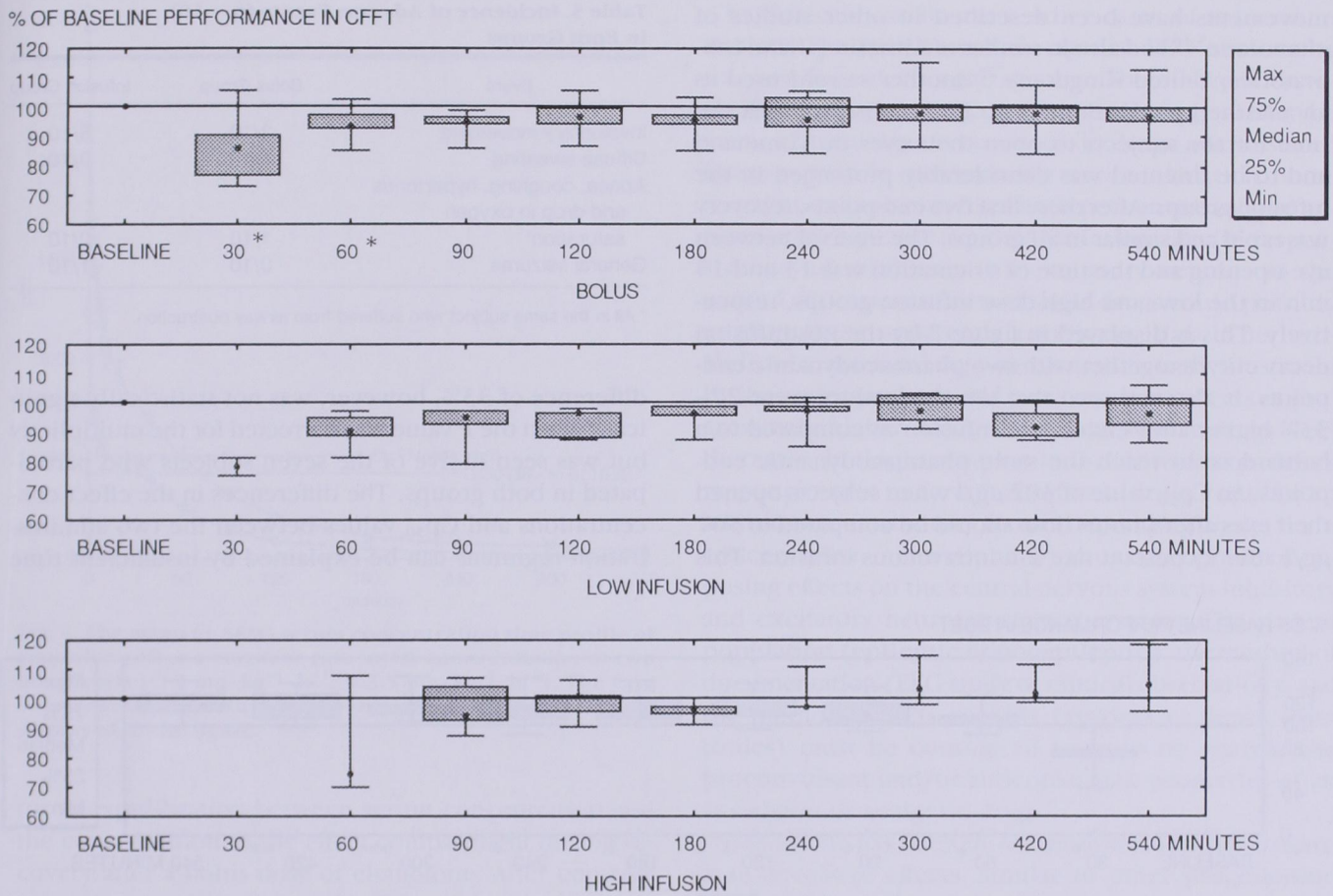

Fig. 5. The median and range of the recovery-time profile for critical flicker fusion threshold after a bolus dose, low-dose infusion, and high-dose infusion expressed as percentage of baseline performance (*$P < 0.05$ between the bolus and infusion groups).

served pharmacodynamic end-points was noted both when the drug was given as a bolus dose and as a constant rate intravenous infusion. The recovery characteristics of eltanolone may thereby be predictable. Most of the subjects had recovered to almost their normal psychomotor condition 60–90 min after injection or end of infusion, although it took 7 h to reach 100% of baseline psychomotor performance. In a comparative study between eltanolone and propofol in outpatients, a similarly delayed onset of early recovery and 20 min later home readiness was seen after eltanolone administration.[6]

The psychomotor tests used have been studied and validated by Nuotto and Korttila *et al.* in several studies. They have found the tests to be useful and among the most sensitive for measuring residual effects of different doses of alcohol, midazolam, or diazepam, and thiopental or propofol.[15–17]

Eltanolone was shown to be a potent induction agent at a dose of 0.75 mg/kg. All subjects fell asleep within one arm-brain circulation time after the bolus dose was given. Loss of the eyelash reflex is not a reliable sign of unconsciousness after administration of eltanolone, so that "loss of verbal contact" was used as the induction criterion.[18] Induction time of eltanolone was thus similar to that found in other studies using the same induction criteria and similar to other intravenous induction agents such as propofol and thiopental.[4–6,19] Anesthesia also was induced in both infusion groups but with different onset times. At an eltanolone serum concentration of 1,200 μg/l all subjects were asleep as judged by the RLS-scoring scale. The hemodynamic effects were minor during induction and infusion and of the same magnitude as seen in other studies.[5,18] The observed involuntary movements were mostly slight and of minor clinical importance. Similar involuntary

movements have been described in other studies of eltanolone[5,18] and also in studies of Althesin (Glaxo Laboratories, United Kingdom),[20] another steroid used as an anesthetic induction agent. It was observed that the time for the subjects to open their eyes on command and to be oriented was considerably prolonged in the infusion groups. After these first two end-points, recovery was rapid and similar in all groups. The interval between eye opening and the time of orientation was 13 and 15 min in the low- and high-dose infusion groups, respectively. This is displayed in figure 7 by the postinfusion decay curves together with two pharmacodynamic end-points. It also was seen that the Cp_{50} values were 27–33% higher after eltanolone infusion as compared to a bolus dose to reach the same pharmacodynamic end-points. An Cp_{50} value of 382 μg/l when subjects opened their eyes after a bolus dose should be compared to 507 μg/l after a constant rate 2-h intravenous infusion. This difference of 33%, however, was not statistically significant when the *P* value was corrected for the multiplicity but was seen in five of the seven subjects who participated in both groups. The differences in the effect concentrations and Cp_{50} values between the two administration regimens can be explained by insufficient time

Table 5. Incidence of Adverse Events (n = 10) in Both Groups

Event	Bolus Group	Infusion Group
Involuntary movement	3/10	6/10
Diffuse sweating	1/10	0/10
Apnea; coughing, hypertonus and drop in oxygen saturation*	1/10	0/10
General seizures	0/10	1/10

* All in the same subject who suffered from airway obstruction.

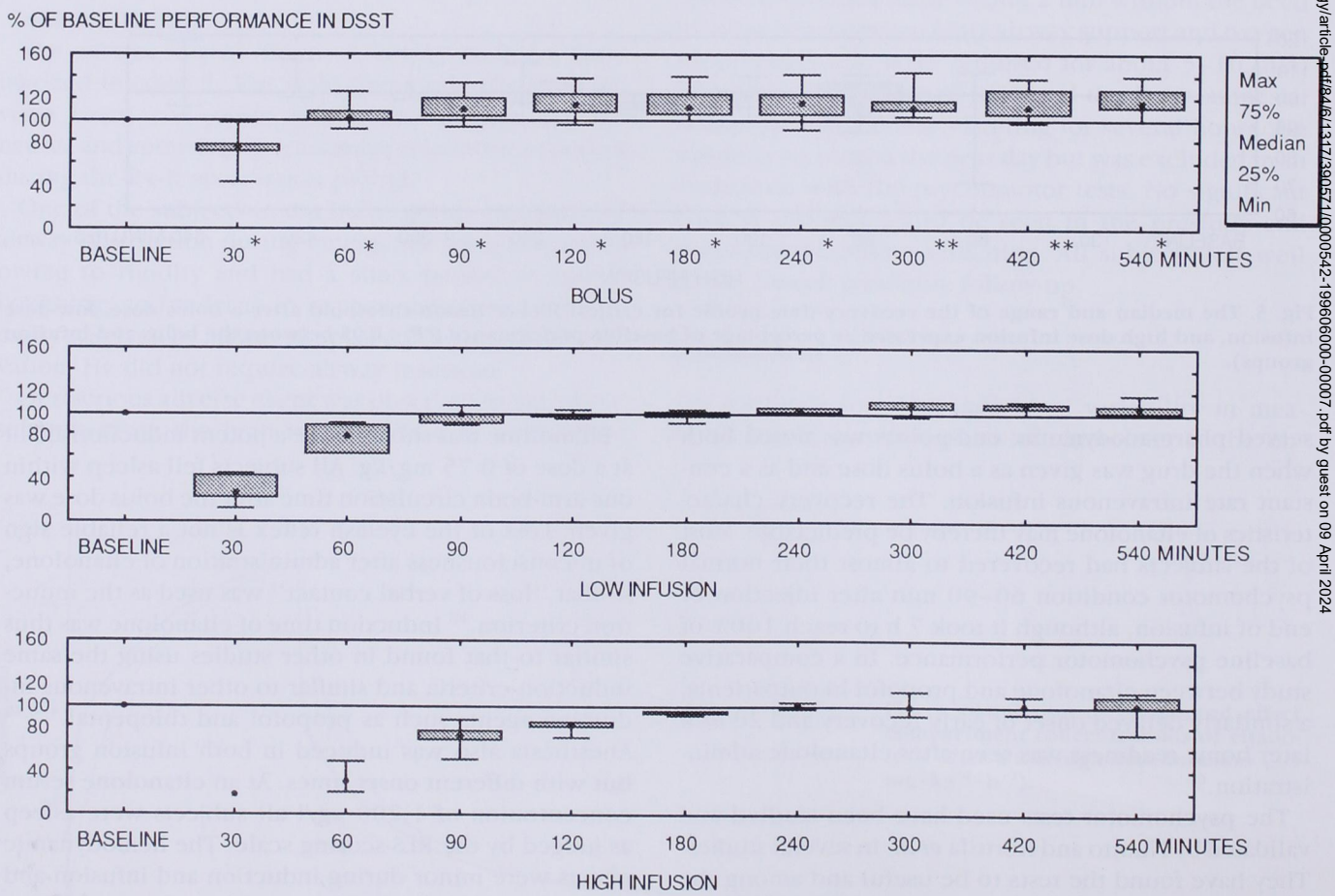

Fig. 6. The median and range of the recovery-time profile for digit symbol substitution test after a bolus dose, low-dose infusion, and high-dose infusion expressed as percentage of baseline performance (*$P < 0.01$ and **$P < 0.05$ between the bolus and infusion groups).

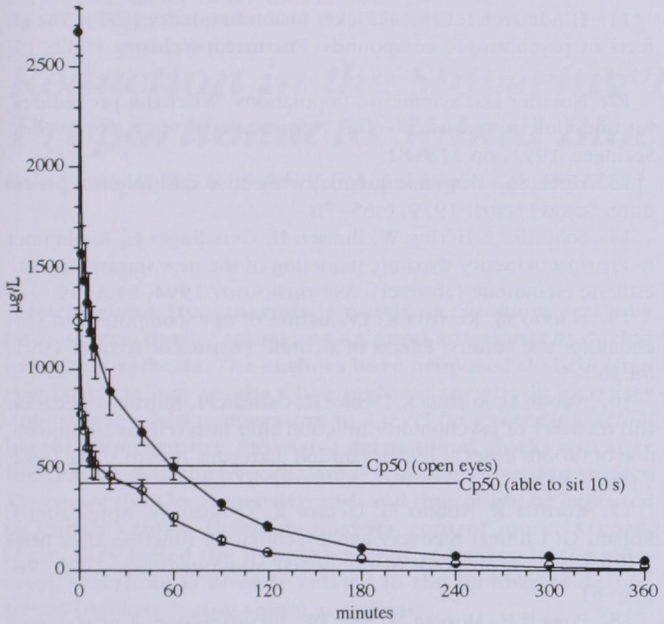

Fig. 7. The mean (± SEM) serum concentration time profile of eltanolone after a constant rate intravenous infusion at two dose levels (○ 2 mg·kg^{-1}·h^{-1}; ● 3.5 mg·kg^{-1}·h^{-1}). The Cp_{50} values associated with two recovery effect end-points also are displayed in the figure.

for an equilibration between serum concentration and the concentration in the effect compartment during recovery after a bolus dose of eltanolone. After constant rate infusion of eltanolone for 2 h resulting in a serum steady-state concentration, sufficient time for a complete equilibration between these two compartments was achieved. Therefore, the serum concentration after infusion better reflected the concentration in the effect compartment. The performed computer simulations of eltanolone concentration in serum and the effect compartment after a bolus dose and during and after a high- and low-dose 2-h infusion also support this hypothesis (figures 3 and 4). Further support of the theory of a slow blood: central nervous system equilibration was the 24% difference in Cp_{50} values between loss of consciousness (628 µg/l) and when consciousness was regained (507 µg/l).

One serious adverse event was observed in this study. A subject given the high infusion dose of eltanolone suddenly developed general seizures that spontaneously resolved within 2 min. The subject was sent to a neurologist for examination. Clinical examination and EEG was normal. The subject refused a computed tomographic scan and further examinations.

In this case, as in many other cases of seizures in conjunction with anesthetic agents, EEG monitoring was not done during the seizure. There have been reports of postoperative convulsions that appeared to be caused by anesthetic or analgesic drugs administered intraoperatively intravenously or *via* inhalation. Some anesthetics appear to have both proconvulsant and anticonvulsant properties.[21,22] Variations in the responsiveness of inhibitory and excitatory neurons to the central depressant effects of these drugs could possibly explain these apparently conflicting data. This variability in neuronal responsiveness is well illustrated by the anticonvulsant and proconvulsant effects of progressively higher doses of local anesthetic drugs. Furthermore, biologic variation in the individual patient's responsiveness to certain anesthetic drugs could be an additional contributory factor. Depending on the brain concentration, centrally active drugs may produce opposing effects on the central nervous system inhibitory and excitatory neurotransmitter systems. The patient population (epileptic or nonepileptic), the method of documentation (EEG study or clinical observation), and the method of EEG analysis (cortical or depth electrodes) must be considered to properly analyze the proconvulsant and/or anticonvulsant properties of an anesthetic or analgesic drug.

Eltanolone has been shown in animals shown to have anticonvulsive effects, similar to other progesterone derivates[23] and there are no reports of seizures in conjunction with eltanolone in the literature.

In summary, the rapid induction caused by a bolus dose makes eltanolone an alternative to currently used induction agents for anesthesia and might therefore be suitable for short-term and outpatient anesthesia. The slow blood:central nervous system equilibration time might be a problem if eltanolone is administered as a maintenance infusion during longer procedures. The study design included a test of drug tolerability, therefore, high doses of eltanolone were administered, and may have led to the long initial recovery times in the infusion groups. If lower doses can be used in conjunction with analgetics and still obtain adequate anesthesia eltanolone also might be an alternative maintenance agent. Further studies are needed to elucidate the dose requirements during surgery and the interactions with opioids. The current information on the relationship of recovery end-points of eltanolone to dose, serum concentration, and time may further support the development of suitable dosage regimens for different uses of this new steroid anesthetic drug.

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