Effects of Eltanolone on Cerebral Blood Flow and Metabolism in Healthy Volunteers

Jørgen Wolff, M.D.,* Peder Carl, M.D.,† Peter Bo Hansen, M.D.,‡ Steffen Høgskilde, M.D.,§
Mogens S. Christensen, M.D., Ph.D.,‖ Mogens B. Sørensen, M.D., Ph.D.#

Background: Eltanolone is a new steroid anesthetic agent that may prove to be useful in clinical practice. The aim of the present study was to evaluate the effects of eltanolone on cerebral blood flow (CBF) and metabolism in healthy volunteers.

Methods: In a randomized cross-over study, eight subjects received intravenous eltanolone 0.6 mg/kg or its vehicle. CBF was measured with the intravenous xenon 133 technique before and 2 and 30 min after administration of eltanolone or vehicle. Cerebral metabolic rate for oxygen (CMR_{O_2}) was calculated as the product of the measured cerebral arteriovenous oxygen content difference and the blood flow.

Results: CBF decreased from a baseline value of 64 ± 4 (mean $\pm$ SD) to 42 ± 6 ml $\cdot$ 100 g^{-1} $\cdot$ min^{-1} at 2 min after administration of eltanolone and only 4% after vehicle. Cerebral oxygen consumption was 4.1 ± 0.4 ml $\cdot$ 100 g^{-1} $\cdot$ min^{-1} at baseline and decreased to 2.7 ± 0.6 at 2 min after eltanolone, whereas metabolism did not change significantly after administration of vehicle. At 30 min CBF and Cerebral metabolic rate for oxygen were 16 and 10% less than baseline values, respectively. Coupling between CBF and Cerebral metabolic rate for oxygen was preserved at all measurements. After administration of eltanolone a significant decrease in mean arterial blood pressure of 6 mmHg and a period of hypoventilation were observed. This did not occur after injection of vehicle.

Conclusions: Eltanolone was shown to reduce cerebral oxygen consumption and blood flow in healthy volunteers. Coupling between metabolism and flow was preserved. (Key

---

* Senior Registrar, Department of Anesthesiology, Bispebjerg Hospital.

† Senior Registrar, Department of Anesthesiology, Hvidovre Hospital.

‡ Registrar, Department of Anesthesiology, Bispebjerg Hospital.

§ Registrar, Department of Anesthesiology, Hvidovre Hospital.

‖ Consultant, Department of Anesthesiology, Bispebjerg Hospital.

Consultant, Department of Anesthesiology, Hvidovre Hospital.

words: Anesthetics, intravenous: eltanolone. Brain: cerebral blood flow; cerebral oxygen consumption.)

THE anesthetic properties of some steroids have been known for several years. Only a few drugs of this class have been introduced into clinical practice, and all preparations have been abandoned because of serious side effects.[1-3]

Eltanolone (3 α-hydroxy-5β-pregnane-20-one, pregnanolone) is a naturally occurring metabolite of progesterone without notable endocrine actions. Its anesthetic effects have been recognized since 1957.[4] However, the drug has not been investigated clinically because of its low water solubility. Eltanolone is now formulated in an oil-and-water emulsion, which is currently in use as a solvent for propofol.

Several reports have shown that the pharmacodynamic properties of eltanolone are similar to those of another steroid anesthetic, althesin, with rapid induction of anesthesia of short duration.[5-7] In addition, a low toxicity of the drug has been found in animals.[8,9] Therefore eltanolone may prove to be a safe and potentially useful new anesthetic agent.

Because of the favorable actions on cerebral blood flow (CBF), oxygen consumption and intracranial pressure, althesin was suitable for use in neuroanesthetic practice,[10-12] until its withdrawal. The close relation in chemical nature and pharmacodynamic profile of althesin and eltanolone may indicate similar effects on cerebral hemodynamics and metabolism.

The purpose of the present study was to evaluate the effects of eltanolone and its vehicle (as placebo) on CBF and cerebral metabolic rate for oxygen (CMR_{O_2}) in healthy volunteers.

Materials and Methods

Eight healthy male volunteers with a mean age of 23 (range 20–25) yr participated in this randomized crossover study. They were within 10% of their ideal body

weight and had no history of previous anesthetic complications, allergy to drugs or alcohol abuse. The trial was conducted in accordance with the Helsinki II Dec laration and approved by the local ethics committee. The experiment was explained to the subjects and informed consent obtained.

They were all in the fasting condition, completely rested and received no premedication before the study.

A radial artery was cannulated with a 20-G catheter for continuous monitoring of mean arterial blood pressure. The electrocardiogram also was recorded. In the contralateral arm the antecubital vein was cannulated for fluid and drug administration. A 16-G venous catheter was inserted with the tip in the internal jugular bulb. The correct position at the base of the skull was verified by radiography.

The subjects were then allowed to rest for 30 min in the supine position and received approximately 1,000 ml normal saline intravenously to compensate for preinvestigational fluid deprivation. They breathed air throughout the procedure and lay in the supine resting position with their eyes closed. Care was taken to reduce the noise level to a minimum.

Volunteers were studied in random order. During each of two sessions at least 1 week apart, each volunteer received an intravenous bolus dose of eltanolone 0 6 mg/kg or an equal volume of vehicle. The injection rate was 0.2 $ml \cdot kg^{-1} \cdot min^{-1}$. The formulation of eltanolone and its vehicle have been described in detail.[5]

Measurements of CBF and CMR_{O_2} were performed before injection of eltanolone or vehicle to determine the baseline values. Two other sets of measurements were started 2 and 30 min after injection of the drug or the vehicle.

Measurements and Calculations

CBF was measured by the intravenous xenon 133 technique with the use of a ten-detector system with integrated computerized data processing (Novo Cerebrograph 10a, Novo Diagnostic Systems, Copenhagen, Denmark).[13,14] Clearance curves from the brain were recorded after injection of 10–20 mCi ^{133}Xe. Analysis of data was performed according to a bicompartmental model and with use of delayed-start fit time for reduction of the air passage artifact.[15] A detector placed over the apex of the right lung was used to obtain data for correcting the effects of ^{133}Xe recirculation.

CBF was calculated as the initial slope index, defined as the decay constant from the early monoexponential part of the fitted clearance curve.[16] CBF values were

averaged for all detectors and expressed as milliliters per 100 g per minute, assuming a blood-brain partition coefficient of 1.0 g/l.

Arterial and jugular venous blood were sampled simultaneously after injection of ^{133}Xe at the time of each CBF measurement. Oxygen and carbon dioxide tensions and pH values were analyzed (ABL 3, Radiometer, Copenhagen, Denmark) and oxygen saturations and hemoglobin concentrations were measured (OSM 3 Hemoximeter, Radiometer).

The arteriovenous oxygen difference was calculated according to the formula

$$AVD_{O_2} = 1.39 \times Hb \times S_{O_2} (A - V)$$
$$+ 0.003 \times P_{O_2}(A - V)$$

where AVD_{O_2} = arteriovenous oxygen difference; Hb = hemoglobin concentration (volume percent); S_{O_2} = oxygen saturation (percent); A = arterial value; V = venous value; and P_{O_2} = oxygen tension (millimeters mercury). CMR_{O_2} was determined as the product of arteriovenous oxygen difference and CBF.

Statistics

All data are reported as means ± SD. The statistical test was a two-way analysis of variance for repeated measurements to detect significant differences between treatments (eltanolone *versus* vehicle), influence of time, and interaction between treatment and time. *Post hoc* pairwise comparisons between the two treatments at different times were performed by Bonferroni's procedure when analysis of variance revealed statistical significance between treatments or significant interaction between treatment and time. In case of significant influence of time, a one-way repeated-measures analysis of variance was performed in the eltanolone group followed by Dunnett's test for *post hoc* comparisons with the baseline values. Significance was assigned at $P < 0.05$.

Results

Figure 1 shows CBF and CMR_{O_2} before and 2 and 30 min after administration of eltanolone or vehicle. The mean CBF decreased 34% from 64 (range 58–69) to 42 (30–48) $ml \cdot 100 \ g^{-1} \cdot min^{-1}$ at 2 min after administration of eltanolone and only 4% at 2 min after vehicle ($P < 0.0001$). At 30 min CBF remained significantly less than either the baseline value ($P < 0.0001$) or the value for vehicle ($P < 0.01$).

Fig. 1. Cerebral blood flow (CBF) and metabolic rate for oxygen (CMR_{O_2}) in eight volunteers before (1) and 2 (2) and 30 (3) min after intravenous administration of a 0.6-mg/kg bolus dose of eltanolone or an equal volume of vehicle. Mean values ± SD are shown below the curves. *P < 0.05 and ***P < 0.0001 compared with baseline values; †P < 0.05, ††P < 0.01, and †††P < 0.0001 compared with corresponding values after administration of vehicle.
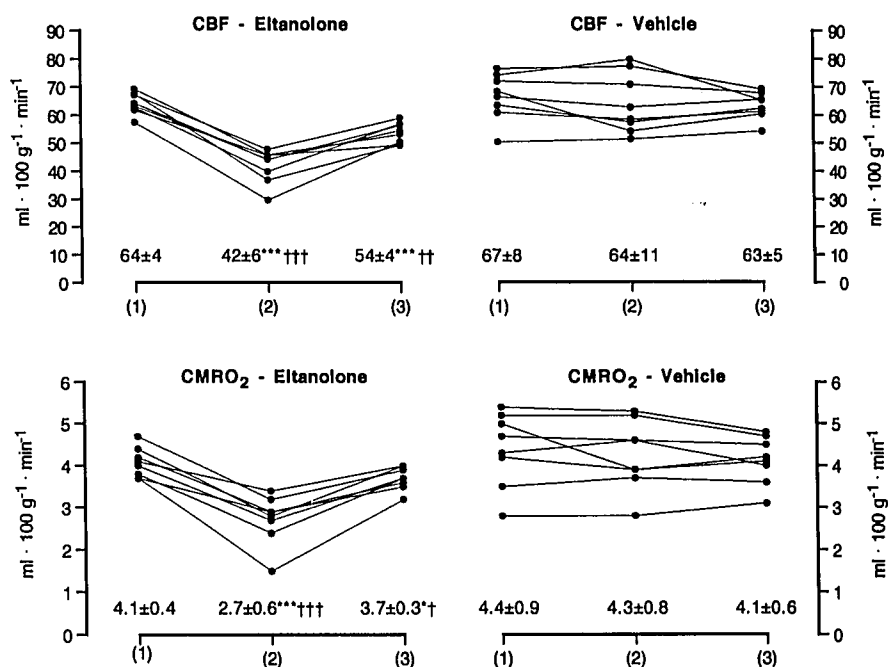
Venous bulb oxygen tension and arteriovenous oxygen difference did not differ significantly between the two groups (table 1). The calculated mean baseline value of CMR_{O_2} was 4.1 (range 3.7–4.7) ml · 100 g⁻¹ · min⁻¹, which decreased to 2.7 (1.5–3.4) ml · 100 g⁻¹ · min⁻¹ after administration of eltanolone (P < 0.0001) whereas CMR_{O_2} did not change after administration of vehicle. At 30 min CMR_{O_2} was 3.7 (3.2–4.0), which was significant compared with the baseline value (P < 0.05) and compared with the corresponding value after vehicle administration (P < 0.05).

The CBF/CMR_{O_2} ratios before and 2 and 30 min after injection of eltanolone were 15.8 ± 1.0, 15.5 ± 2.4 and 14.6 ± 1.1 respectively (n..s.) The corresponding values after injection of vehicle were 15.6 ± 3.2, 15.3 ± 2.6 and 15.5 ± 2.1 (n. s.). The between-group comparison also was statistically insignificant.

The mean arterial blood pressure decreased 7% after administration of eltanolone (P < 0.05) (table 1). Only minor changes were seen after injection of vehicle.

Blood gas values are given in table 1. Arterial oxygen tension did not vary between the two groups at baseline but decreased significantly after administration of eltanolone. The lowest value of arterial oxygen tension was 68 mmHg in one subject. No oxygen had to be administered, and oxygen tensions were normal within 30 min. A short period of hypoventilation was observed

after induction with eltanolone, as indicated by an increase in arterial carbon dioxide tension (P < 0.0001). The highest value for arterial carbon dioxide tension obtained at 2 min was 47 mmHg in one subject. Values at 30 min were normal. No changes in arterial carbon dioxide tension occurred after administration of vehicle.

The only adverse effects of eltanolone were seen in one case during the recovery from anesthesia. Involuntary movements with increased tone in all the limbs were observed for a period of about 3 min. The subject had total amnesia for the event.

Discussion

Results from preliminary volunteer and clinical trials have shown that administration of an intravenous bolus dose of eltanolone 0.5–0.6 mg/kg produce a state of anesthesia within approximately one min and with a duration of 7–15 min. Induction of anesthesia has been smooth and reliable although involuntary movements have been observed.[5–7] A minor decrease in arterial blood pressure and a short period of hypoventilation have been registered. In summary, the pharmacodynamic properties of eltanolone seemed to be similar to those of althesin.[5]

Table 1. Mean Arterial Blood Pressure, Arterial P_{O_2} and P_{CO_2}, Jugular Venous Bulb P_{O_2}, and Arteriovenous Oxygen Content Difference before (1) and at 2 (2) and 30 min (3) after an Intravenous Bolus Dose of 0.6 mg/kg Eltanolone or an Equal Volume of the Vehicle in Eight Volunteers

	Eltanolone			Vehicle		
	1	2	3	1	2	3
MAP (mmHg)	83 ± 6	77 ± 7*	77 ± 7*	83 ± 5	81 ± 4	84 ± 5
Pa_{O_2} (mmHg)	99 ± 13	80 ± 6†§	103 ± 7	98 ± 4	98 ± 5	100 ± 4
Pa_{CO_2} (mmHg)	41 ± 2	44 ± 2‡§	41 ± 2	41 ± 2	41 ± 2	41 ± 2
Pv_{O_2} (mmHg)	34 ± 1	31 ± 4	32 ± 1	34 ± 4	33 ± 3	33 ± 2
$AVDO_2$ (vol%)	6.3 ± 0.4	6.5 ± 1.1	6.9 ± 0.6	6.6 ± 1.1	6.7 ± 1.0	6.6 ± 0.7

Values are mean ±SD

* $P < 0.05$, †$P < 0.001$, ‡$P < 0.0001$ versus baseline value (1). §$P < 0.0001$ versus vehicle.

Preliminary pharmacokinetic studies have shown a terminal elimination half life of eltanolone between 0.9 and 1.4 h, probably based on hepatic clearance.[5] By using a three-compartment model a rapid distribution phase ($T_{1/2\alpha}$ 0.3–2 min) followed by a β phase ($T_{1/2\beta}$ 12–29 min) and a terminal half-life between 1.2–3.5 h have been demonstrated.[17]

The precise mechanism of action of steroid anesthetic agents has not been established. However, the central pharmacologic effects have been proposed to be mediated by enhancing the synaptic transmission of γ-aminobutyric acid at the receptor level.[18,19]

In the present study we found a mean decrease of 34% (26–48%) in the measured values of CBF after injection of eltanolone. The cerebral venous oxygen saturation did not change significantly. Consequently, a corresponding reduction in CMR_{O_2} of a similar magnitude was calculated (17–59%) after administration of eltanolone ($P < 0.0001$) whereas CMR_{O_2} did not change significantly after injection of vehicle. At 30 min the mean CBF was 16% less than baseline ($P < 0.0001$), and the reduction in mean CMR_{O_2} at that time was 10% ($P < 0.05$). Therefore, the main effect on cerebral circulation and metabolism of eltanolone seemed to be of brief duration with a minor residual action after 30 min. The coupling of CBF and metabolism (CBF/CMR_{O_2} ratio) was found to be preserved. This may indicate that the primary action of eltanolone was a depression in cerebral metabolic oxygen consumption and a subsequent equivalent decrease in oxygen supply. Similar effects on CBF and CMR_{O_2} have been demonstrated for althesin[20] and other intravenous anesthetic agents and sedatives.[21-24]

The cerebral vascular reactivity to changes in carbon dioxide tension was not evaluated in the present study.

However, assuming a preserved carbon dioxide response, as observed with most other intravenous anesthetic agents, including althesin,[20] the decrease in CBF would have been enhanced if values were corrected for the observed hypercapnia after administration of eltanolone.

According to the protocol the subjects were left unstimulated during the trial. By observation, unconsciousness was attained within 70 s and lasted 9–17 min. At 30 min all volunteers were awake and oriented although most of the subjects were still drowsy at that time. The decrease in CMR_{O_2} and CBF at 2 min with a minor residual effect at 30 min fully agreed with the observed clinical actions of eltanolone and with the pharmacokinetic data.

A slight decrease in mean arterial blood pressure was observed after administration of eltanolone, but in no case did it reach values below the generally accepted lower limit of cerebral autoregulation (60 mmHg) in normotensive individuals. Despite a significant decrease in arterial oxygen tension, observed in all subjects, this was unlikely to account for any change in CBF.

The intravenous ^{133}Xe technique with the use of initial slope index have been shown to be a reliable and reproducible method of estimation CBF.[14] However, although the index represents clearance from both the cerebral gray and white matter, it is dominated by the fast flow gray matter. Therefore, initial slope index mainly reflects CBF changes in these areas. The same applies to the calculation of CMR_{O_2} and may give rise to a systematic error if the drug induced alterations mainly took place in the cerebral white matter regions. However, it seems unlikely that the parallel changes in CBF and CMR_{O_2} predominantly should be located to the gray and white matter, respectively.

Based on the clinical actions and pharmacokinetic data one may anticipate that the cerebrovascular and metabolic effects were already extensive at 2 min after termination of eltanolone administration. Initial slope index was estimated at 30–90 s from the fitted ^{133}Xe clearance curve. During this period it was assumed that the cerebral actions of eltanolone were approximately constant. These suppositions were in agreement with the onset of effects on CBF and CMR_{O_2} after an intravenous bolus dose of althesin in baboons.[25]

In conclusion, eltanolone was shown to have a depressant effect on cerebral oxygen consumption and blood flow. The ratio CBF/CMR_{O_2} remained unchanged, indicating a preserved coupling of flow and oxygen metabolism. Although the demonstrated cerebrovascular and metabolic properties of eltanolone are appropriate for use in neuroanesthesia and intensive care, further investigations are required to establish the possible future role of eltanolone in clinical anesthetic practice including patients with neuropathologic conditions.

References

1. Howland WS, Boyan CP, Wang K-C: The use of a steroid (Viadril) as an anesthetic agent. ANESTHESIOLOGY 17:1–8, 1956

2. Clarke RSJ, Dundee JW, Carson IW: Some aspects of the clinical pharmacology of althesin. Postgrad Med J 48(suppl 2):62–65, 1972

3. McNeill HG, Clarke RSJ, Dundee JW: Minaxolone: A new water soluble steroid anaesthetic. Lancet 2:73–74, 1979

4. Figor SK, Kodet MJ, Bloom BM, Agnello EJ, P'An SY, Laubach GD: Central activity and structure in a series of water-soluble steroids. J Pharmacol Exp Ther 119:299–309, 1957

5. Carl P, Høgskilde S, Nielsen JW, Sørensen MB, Lindholm M, Karlen B, Bäckstrøm T: Pregnanolone emulsion: A preliminary pharmacokinetic and pharmacodynamic study of a new intravenous anaesthetic agent. Anaesthesia 45:189–197, 1990

6. Powell H, Morgan M, Sear JW: Pregnanolone: A new steroid intravenous anaesthetic—Dose-finding study. Anaesthesia 47:287–290, 1992

7. Gray HSTJ, Holt BL, Whitaker DK, Eadforth P: Preliminary study of a pregnanolone emulsion (Kabi 2213) for i. v. induction of general anaesthesia. Br J Anaesth 68:272–276, 1992

8. Høgskilde S, Wagner J, Carl P, Bredgaard Sørensen M: Anaesthetic properties of pregnanolone emulsion: A comparison with alphaxolone/alphadolone, propofol, thiopentone and midazolam in a rat model. Anaesthesia 42:1045–1050, 1987

9. Høgskilde S, Nielsen JW, Carl P, Sørensen MB: Pregnanolone emulsion: A new steroid preparation for intravenous anaesthesia—An experimental study in mice. Anaesthesia 42:586–590, 1987

10. Turner JM, Coroneos NJ, Gibson RM, Powell D, Ness MA, McDowall DG: The effect of althesin on intracranial pressure in man. Br J Anaesth 45:168–171, 1973

11. Rasmussen NJ, Rosendal T, Overgaard J: Althesin in neurosurgical patients: Effects on cerebral hemodynamics and metabolism: Acta Anaesthesiol Scand 22:257–269, 1978

12. Bendtsen A, Kruse A, Madsen JB, Astrup J, Rosenørn J, Blatt-Lyon B, Cold GE: Use of a continuous infusion of althesin in neurosurgery: Changes in cerebral blood flow, cerebral metabolism, the EEG and plasma alphaxalone concentration. Br J Anaesth 57:369–374, 1985

13. Larsen B, Christensen MS: A system for monitoring the CBF based on the Xenon-133 i. v. technique. rCBF Bull 2:27–31, 1981

14. Schroeder T, Holstein P, Lassen NA, Engell HC: Measurement of cerebral blood flow by intravenous Xenon-133 technique and a mobile system: Reproducibility using the Obrist model compared to total curve analysis. Neurol Res 8:237–241, 1986

15. Obrist WD, Thomson HK Jr, Wang HS, Wilkerson WE: Regional cerebral blood flow estimated by Xenon-133 inhalation. Stroke 6:245–256, 1975

16. Risberg J, Ali Z, Wills EL, Halsey JH: Regional cerebral blood flow by Xenon-133 inhalation: Preliminary evaluation of an initial slope index in patients with unstable flow compartments. Stroke 6:142–148, 1975

17. Carl P, Lang-Jensen T, Bach V, Jacobsen J, Sørensen MB, Grälls M, Widlund L: Pharmacokinetics and pharmacodynamics of eltanolone (pregnanolone), a new steroid intravenous anaesthetic, in humans. Acta Anaesthesiol Scand (in press)

18. Turner DM, Ransom RW, Yang JSJ, Olsen RW: Steroid anesthetics and naturally occurring analogs modulate the gamma-amino butyric acid receptor complex at a site distinct from barbiturates. J Pharmacol Exp Ther 248:960–966, 1989

19. Majewska MD, Harrison NL, Schwartz RD, Barker JL, Paul SM: Steroid hormone metabolites are barbiturate-like modulators of the GABA receptor. Science 232:1004–1007, 1986

20. Sari A, Maekawa T, Tohjo M, Okuda Y, Takeshita H: Effects of althesin on cerebral blood flow and oxygen consumption in man. Br J Anaesth 48:545–549, 1976

21. Pierce EC, Lambertsen CJ, Deutsch S, Chase P, Linde HW, Dripps RD, Price HL: Cerebral circulation and metabolism during thiopental anesthesia and hyperventilation in man. J Clin Invest 41:1664–1671, 1962

22. Stephan H, Sonntag H, Schenk HD, Kohlhausen S: Effects of Disoprivan on cerebral blood flow, cerebral oxygen consumption and cerebral vascular reactivity. Anaesthesist 36:60–65, 1987

23. Renou AM, Vernhiet J, Macrez P, Constant P, Billerey J, Khadaroo MY, Caillé JM: Cerebral blood flow and metabolism during etomidate anaesthesia in man. Br J Anaesth 50:1047–1051, 1978

24. Forster A, Juge O, Morel D: Effects of midazolam on cerebral blood flow in human volunteers. ANESTHESIOLOGY 56:172–176, 1982

25. Pickerodt VWA, McDowall DG, Coroneos NJ, Keaney NP: Effect of althesin on cerebral perfusion, cerebral metabolism and intracranial pressure in the anaesthetized baboon. Br J Anaesth 44:752–756, 1972