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Relative Potency of Eltanolone, Propofol, and Thiopental for Induction of Anesthesia

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Background: **The primary purpose of this investigation was to determine the relative potency of eltanolone, a new steroid hypnotic, and propofol and thiopental when used for induction of general anesthesia. In addition, the induction characteristics of propofol and eltanolone were compared.**

Methods: **One hundred seventy-five patients, premedicated with lorazepam 1 mg orally, randomly received one of six different doses of either eltanolone or propofol. The probability of successful induction (defined as not responsive to verbal commands within 2 min) was related to the logarithm of the dose for each drug by means of logistic regression analysis. Estimates of ED_{50} and ED_{95} for each drug were obtained. The incidence of side effects was compared for eltanolone and propofol. The potency of thiopental was determined in a parallel study, using an identical methodology in 105 patients receiving one of seven different doses of the barbiturate.**

Results: **The relative potency of eltanolone was 3.2 times (95% confidence interval 2.7–3.8) greater than propofol and 6.0 times (5.3–6.9) greater than thiopental. ED_{50} and ED_{95} values for eltanolone were 0.46 (0.40–0.52) and 0.82 (0.68–1.28) $mg \cdot kg^{-1}$, respectively. Compared to propofol, induction of anesthesia with eltanolone is characterized by a lower incidence of injection pain (3.5% *vs.* 58%) and apnea (1.2% *vs.* 11.2%).**

Conclusions: **Eltanolone appeared to be an effective induction agent that is 3.2 times more potent than propofol and 6 times more potent than thiopental. Its use was associated with less pain on injection than was propofol. (Key words: Anesthetics, intravenous: eltanolone; propofol; thiopental. Potency: induction.)**

SEVERAL structurally related pregnanes possess sedative–hypnotic activity while lacking any endocrinologic actions. Of the various pregnanes, pregnanolone (3α-hydroxy-5β-pregnan-20-one), a naturally occurring metabolite of progesterone, has the greatest hypnotic potency in mice.[1] As a result of its low water solubility, pregnanolone has been formulated as an emulsion of 4 mg pregnanolone, 200 mg purified soybean oil, 70 mg diacetyl monoglycerides, 18 mg purified egg phospholipids, 17 mg glycerol, and sufficient sodium hydroxide to adjust *p*H to approximately 8, *pro* 1 ml emulsion.

Pregnanolone (eltanolone, Kabi 2213, Kabi Pharmacia, Sweden) is undergoing phase-2 clinical investigation as an hypnotic agent for induction of general anesthesia. We designed a controlled, single-blind, randomized study to determine the relative potency and safety of eltanolone when compared to propofol (and thiopental) for induction of anesthesia in healthy, premedicated patients.

Materials and Methods

The study protocol was approved by the Committee for Medical Ethics/Clinical Trials of the Faculty of Medicine of the Catholic University of Leuven. Written, informed consent was obtained from all patients.

Comparison Between Eltanolone and Propofol

One hundred seventy-five patients of both sexes, 18–50 yr of age, ASA physical status 1 or 2, were included in the study. Patients who had documented drug allergy, who were obese (> 120% of ideal body weight‖), or who had current known alcohol, drug, or medication abuse were excluded. We also excluded patients who had participated in clinical studies of nonapproved

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drugs in the 2-week period before admission or who had participated earlier in this study.

All patients were premedicated with lorazepam 1.0 mg orally, administered 0.5–2 h before induction of anesthesia. Initially, 150 patients were randomly assigned to receive five different doses of either eltanolone or propofol. The first 25 patients received eltanolone 0.4, 0.5, 0.6, 0.7, or 0.8 $mg \cdot kg^{-1}$ or propofol 1.25, 1.5, 1.75, 2.0, or 2.25 $mg \cdot kg^{-1}$. After the first 25 patients had been entered into the study, the investigators suspected that the highest dose of each drug would induce unconsciousness in 100% of the patients, which would interfere with the methodology used to determine the relative potency of the drugs. Therefore, the lowest and highest doses of eltanolone and propofol were decreased to 0.3 and 0.7 $mg \cdot kg^{-1}$ and 1.0 and 2.0 $mg \cdot kg^{-1}$, respectively. Thus, the final 150 patients were randomly assigned to ten groups of 15 patients, each receiving 0.3, 0.4, 0.5, 0.6, or 0.7 $mg \cdot kg^{-1}$ of eltanolone, or 1.0, 1.25, 1.5, 1.75, or 2.0 $mg \cdot kg^{-1}$ of propofol.

The dose of study drug was administered over 30 s into a large forearm vein into a freely running infusion of Ringer's lactate solution. In each patient the effect was evaluated by the same investigator, to whom the drug and the dose remained unknown. The patient was asked to count aloud and to hold a weighted syringe firmly for as long as possible. Successful induction of anesthesia was defined as loss of consciousness, described as the state when the patient no longer responded to verbal commands ("open your eyes" or "squeeze my fingers"). The time interval from the start of the injection of study drug to unconsciousness was recorded. In addition, the time intervals to the moment the patient stopped counting and dropped the weighted syringe, as well as the presence or absence of these responses, were recorded. Finally, the eyelash reflex was tested if the patient was unconscious.

The primary efficacy variable was induction of anesthesia within 2 min after the start of administration of the study drug. Safety was evaluated by examining the effect of the study drugs on blood pressure, heart rate, and respiration and by noting any eventual occurrence of untoward side effects. Blood pressure (automatic blood pressure measurement, Colin THE BP 1001, Nippon Colin, Japan), heart rate, and hemoglobin oxygen saturation (pulse oximetry, Nellcor N 2500, Hayward, CA) were recorded before and at 1-min intervals during the first 3 min after the start of drug administration. The occurrence of respiratory side effects (*e.g.*, coughing or apnea) was noted. Apnea was defined as the absence for more than 60 s of clinically perceptible respiratory movements. If the patient was apneic or if the hemoglobin oxygen saturation decreased to < 90%, assisted ventilation was started. The presence of other side effects (*e.g.*, pain or discomfort during injection [graded as mild, moderate, or severe], excitatory phenomena, myoclonus or muscle movements, and cutaneous reactions [such as rash]) was noted. No additional medication was administered during the 3-min postinjection observation period. If the patient was still conscious after the 3-min observation period, an additional dose of the assigned hypnotic was administered until unconsciousness was achieved. All patients were interviewed approximately 24 h after the administration of the study drug.

Data on all patients were included in the analysis of side effects and efficacy. With regard to the primary efficacy endpoint, however, the first 25 patients and 1 patient of the final 150 who received a miscalculated dose of propofol were not used in the potency determination.

Determination of the Potency of Thiopental

Patients who were reluctant to receive a nonapproved drug were asked to participate in a parallel study to determine the potency of thiopental. One hundred five consenting patients were randomly assigned to seven groups of 15 patients each, receiving thiopental 2.0, 2.2, 2.4, 2.6, 2.8, 3.2, or 3.4 $mg \cdot kg^{-1}$, administered as a 5-$mg \cdot ml^{-1}$ solution over 30 s. The induction was evaluated using an identical efficacy criterion (loss of response to verbal commands within 2 min after the start of administration of the study drug), by the same observer, who was blinded as to the administered dose of thiopental. Comparisons between the induction characteristics of thiopental and those of the other two induction agents were not reported because of the dissimilarity in the degree of observer blinding.

Statistical Methodology

The probability of successful induction of anesthesia (the primary efficacy variable) was related to the logarithm of the dose for each drug by means of a logistic regression analysis.[2] This logistic regression model was used for estimating the clinical potency of eltanolone relative to propofol and thiopental with respect to induction of anesthesia. These results are presented as point estimates and 95% confidence intervals. Estimates of the dose effective in 50% and 95% of the subjects

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(ED_{50} and ED_{95}, respectively) for each drug also were obtained using the logistic regression model. The 95% confidence interval for the estimates was obtained according to Fieller's theorem.[3] The statistical analysis of relative potency was performed using the Statistical Analysis Software, PROC LOGIST, which includes tests for parallelism of the curves.

Other comparisons were made only for patients treated with either eltanolone or propofol. Adverse events are summarized in a frequency table (see table 3, below), and comparisons between groups were performed using Fisher's exact test (two-tailed). Relative changes in heart rate and blood pressure were compared with baseline values using a paired Student's *t* test with Bonferroni's correction. Comparisons of the hemodynamic changes between groups were made using mean values and 95% confidence limits and a two-tailed Student's *t* test. The relative potency, ED_{50}, and ED_{95} are expressed as mean values and 95% confidence intervals. Demographic data and hemodynamic changes are expressed as mean values ± standard deviation. The time interval to the different endpoints of induction are expressed as a range.

Results

Thirty-eight male and 137 female ASA physical status 1 or 2 patients received eltanolone or propofol, and 30 male and 75 female patients were studied to determine the dose–effect relationship of thiopental. The mean age of patients in the three study groups was similar (eltanolone 33 ± 9 yr, propofol 34 ± 7 yr, and thiopental 36 ± 8 yr) (no significant statistical difference).

Figure 1 describes the probability relationship between the logit transformation of a successful induction and the logarithm of the dose of study drug. This method was used to modify the sigmoid shape of the dose–response curve into a straight line. From the relative distance between the curves, the potency ratio can be calculated. The relative potency of eltanolone compared to propofol was 3.2 (95% confidence interval 2.7–3.8). The relative potency of eltanolone to thiopental was 6.0 (5.3–6.9). The calculated ED_{50} and ED_{95} (and 95% confidence interval) were 0.46 (0.40–0.52) and 0.82 (0.68–1.28) $mg \cdot kg^{-1}$ for eltanolone, 1.47 (1.29–1.65) and 2.68 (2.16–4.90) $mg \cdot kg^{-1}$ for propofol, and 2.75 (2.58–2.97) and 4.13 (3.16–5.59) $mg \cdot kg^{-1}$ for thiopental.

When the induction was successful, the time interval from the start of the administration of eltanolone and propofol was similar and unrelated to the administered dose. Moreover, loss of consciousness always occurred within the first 2 min of the observation period. If the patients stopped counting or dropped the weighted syringe, it occurred 45–60 and 54–68 s, respectively, after the start of the administration of eltanolone. In the propofol group, patients stopped counting and dropped the weighted syringe 42–54 and 48–58 s, respectively, after the start of drug administration. The number of patients who stopped counting, dropped the weighted syringe, lost the eyelash reflex, and did not respond to verbal commands for each different dose of eltanolone or propofol is summarized in table 1.

All 175 patients receiving eltanolone or propofol were included in the evaluation of side effects. Table 2 summarizes the percent change in blood pressure and heart rate (mean values ± SD) relative to the measurements before the administration of each dose of eltanolone and propofol. The decrease in systolic and diastolic blood pressure was significantly greater at 3 min after injection of propofol (−14.9 ± 8.8% and −18.5 ± 11.3%, respectively), than after injection of eltanolone (−9.9 ± 8.2% and −11.2 ± 11.2%, respectively) ($P < 0.001$). Administration of eltanolone was associated with a significant increase in heart rate, which was maximal 1 min after injection (11.4 ± 14.7%) ($P < 0.001$). In contrast, no significant changes in heart rate were noted after propofol.

Table 3 summarizes the adverse events observed during induction. The incidence of apnea (> 60 s) was greater in the propofol group than in the eltanolone group ($P = 0.009$). A mild patchy cutaneous rash over the thoracic area, observed in one patient in each group, disappeared spontaneously in less than 5 min. One patient presented with an excitatory reaction (phonation of incoherent sounds and words) after the administration of eltanolone 0.3 $mg \cdot kg^{-1}$. Later the patient did not recall the event. After an initially successful induction, two patients who had received eltanolone 0.6 $mg \cdot kg^{-1}$ exhibited involuntary muscle movements 2–3 min after drug administration. These muscle movements lasted 30 s to 2 min. One patient exhibited excitatory reactions (*e.g.*, movement, opening of the eyes, and phonation) 3 min after the administration of propofol 1.75 $mg \cdot kg^{-1}$. Fifty-eight percent of the propofol-treated patients experienced mild to severe pain in the arm during the initial injection of propofol. In contrast, only three patients (3.5%) com-

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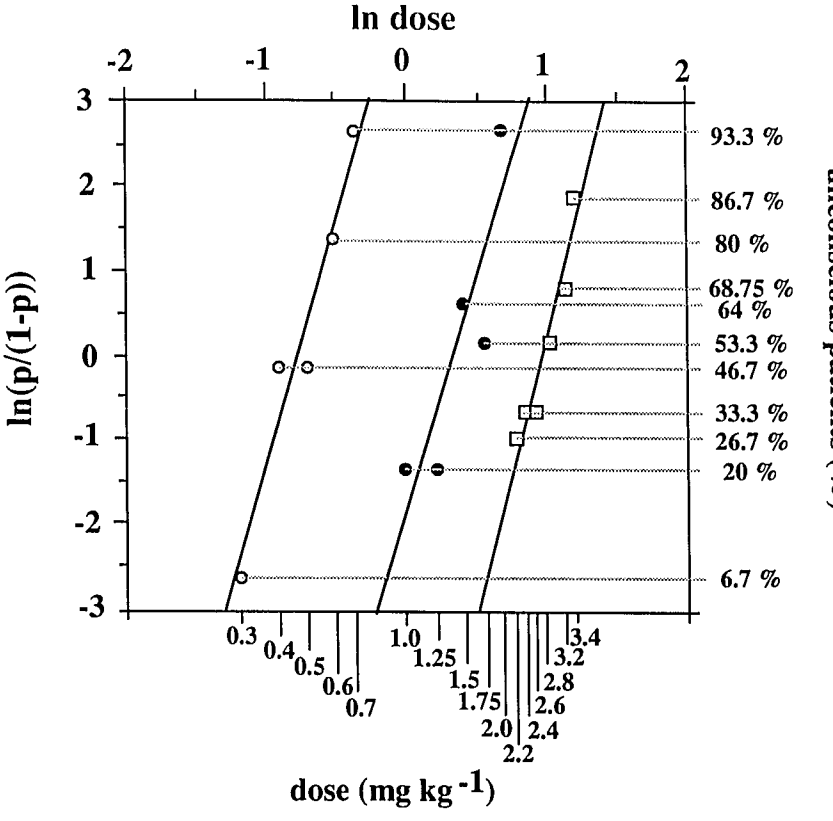

Fig. 1. Relationship between the logit transformation of a successful induction probability (p) (the percentage of patients not responding to verbal commands) and the logarithm of the dose of eltanolone (open circles), propofol (filled circles), and thiopental (squares).

plained of mild pain during the injection of eltanolone. No postoperative signs of thrombophlebitis were observed in either group.

Discussion

Because eltanolone is not yet approved for use as a continuous infusion for maintenance of anesthesia, it was impossible to study its relative potency using steady-state conditions. Instead, we used a clinically relevant induction method. It has been shown previously that the relative potency of induction agents varies when different endpoints of anesthesia are considered.[4] In this study we used a clinically relevant time interval (loss of consciousness within 2 min) as our primary efficacy criterion. The loss of verbalization and of active muscle tone appeared to occur at subanesthetic levels of propofol or eltanolone (*i.e.*, when patients were still responding to verbal commands). In contrast, eyelash reflex remained present in patients in whom anesthesia was judged to be successfully induced with these hypnotic drugs. However, it has been reported that loss of the eyelash reflex is not a reliable endpoint for induction of anesthesia with propofol or eltanolone.[5–7]

The use of lorazepam for preanesthetic medication certainly influenced the calculation of the ED_{50} and ED_{95}. We also acknowledge that potential differences in the interaction of lorazepam with the different induction agents may have had an effect on the potency ratio of the three hypnotic drugs. Nevertheless, the investigators chose to administer the same premedication in every study patient to conform to the clinical practice at their institution for a patient population similar to the study population. Future investigations, including dose–response studies in nonpremedicated patients, will be necessary to clarify the comparative pharmacology of eltanolone and other induction agents. Using a similar methodology, Grounds *et al.* studied the potency ratio of thiopental and propofol.[8] Although only atropine was used for premedication, the calculated ED_{50} and ED_{95} for thiopental (2.22 and 3.56 $mg \cdot kg^{-1}$, respectively) and for propofol (1.39 and 2.22 $mg \cdot kg^{-1}$, respectively) were consistently lower than in the current study, suggesting that these investigators used a somewhat different

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Table 1. Responses of Patients at Each Dose of Eltanolone and Propofol

Drug	Dose ($mg \cdot kg^{-1}$)	Response			
		Stopped Counting	Dropped Weighted Syringe	Unconscious (No Response to Verbal Commands)	Lost Eyelash Reflex
Eltanolone	0.3	7/15	4/15	1/15	0/15
	0.4	15/17	10/17	8/17	1/17
	0.5	18/18	14/18	10/18	3/18
	0.6	17/17	17/17	14/17	1/17
	0.7	17/17	17/17	16/17	11/17
	0.8	2/2	2/2	2/2	2/2
Propofol	1.0	6/15	5/15	3/15	0/15
	1.25	10/18	11/18	5/18	2/18
	1.5	16/19	15/19	11/19	6/19
	1.75	18/18	17/18	10/18	9/18
	2.0	16/16	16/16	15/16	11/16
	2.25	3/3	3/3	3/3	2/3

endpoint in defining unconsciousness. Using Dixon's up-and-down method and loss of eyelash reflex as the endpoint for induction of anesthesia, Powell *et al.* reported the ED_{50} of eltanolone to be 0.44 $mg \cdot kg^{-1}$ in patients premedicated with morphine 0.1 $mg \cdot kg^{-1}$ and atropine.[6] Induction of anesthesia was accomplished in a median time of 65 s (range 32–96 s), which is identical to the findings of the current investigation.

Some observer bias may have existed in the study because of the partial blinding. For the comparison between eltanolone and propofol, the observer of effects was unaware of the drug and the dose that had been given. Although the presence of a much greater incidence of injection pain with propofol may have biased the study, this difference was unexpected before data analysis in view of the similarity of the solvent. For the thiopental-treated patients, the observer was blinded only regarding the dose that had been administered. These data were used only to construct the dose–response curve.

Although gender-related differences may exist in the pharmacologic properties of highly lipophilic drugs, to date no data on this question are available with regard to eltanolone. The gender distribution in the different dose-groups in the current study was similar. Moreover, successful induction of anesthesia was accomplished in a similar percentage of male and female patients with each study drug.

The modest decrease in blood pressure and increase in heart rate that were observed after administration of

Table 2. Heart Rate and Blood Pressure Changes Compared to Baseline 3 Min after the Administration of Eltanolone or Propofol

Drug	Dose ($mg \cdot kg^{-1}$)	Heart Rate Change (%)	Systolic Pressure Change (%)	Diastolic Pressure Change (%)
Eltanolone	0.3	+4.3 ± 12.3	−7.8 ± 7.6	−9.1 ± 10.5
	0.4	+3.4 ± 13.3	−7.2 ± 9.8	−9.4 ± 10.9
	0.5	−0.2 ± 11.1	−11.1 ± 7.5	−16.1 ± 8.9
	0.6	+12.5 ± 15.8	−9.7 ± 8.4	−13.8 ± 12.1
	0.7	+6.7 ± 15.2	−12.6 ± 7.5	−8.0 ± 12.7
Propofol	1.0	−2.6 ± 12.2	−10.7 ± 10.8	−15.0 ± 12.9
	1.25	0.7 ± 14.4	−15.0 ± 7.2	−19.8 ± 10.0
	1.50	−2.6 ± 15.1	−15.4 ± 10.2	−16.9 ± 10.2
	1.75	−4.1 ± 19.9	−14.6 ± 7.6	−17.4 ± 11.2
	2.0	−3.4 ± 16.7	−17.2 ± 7.7	−21.9 ± 13.0

Values are mean ± SD.

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Table 3. Adverse Events Observed during Induction of Anesthesia with Eltanolone or Propofol

Adverse Event	Eltanolone (n = 86)	Propofol (n = 89)
Apnea (>60 s)	1 (1.2%)	10 (11.2%)*
Wheezing	2 (2.3%)	1 (1.1%)
Coughing	1 (1.2%)	1 (1.1%)
Treated hypotension	1 (1.2%)	1 (1.1%)
Cutaneous rash	1 (1.2%)	1 (1.1%)
Excitation	1 (1.2%)	1 (1.1%)
Involuntary muscle movements	2 (2.3%)	—
Injection pain	3 (3.5%)	52 (58%)†

Values are numbers (and percentages) of patients.

* $P = 0.009$ between groups.

† $P < 0.001$ between groups.

eltanolone are in agreement with previous findings in patients[6] and in volunteers.[7] Surprisingly, the changes in blood pressure and heart rate were independent of the dose of the induction agents and were identical in patients in whom anesthesia was successfully induced compared to patients who did not completely lose consciousness. The decrease in blood pressure produced by eltanolone appeared to be less than that after an equipotent dose of propofol, although the difference (approximately 10% *vs.* 15%) was too small to be considered clinically important. The side effects that we observed were similar to those described by Powell *et al.*[6] In contrast to our findings, those investigators reported a 12% incidence of apnea after eltanolone.

In conclusion, eltanolone appears to be an effective induction agent in healthy adults. Few side effects were observed. The relative hypnotic potency of eltanolone: propofol was 3.2:1 (95% confidence interval 2.7–3.8) and for eltanolone:thiopental was 6.0:1 (5.3–6.9). The calculated ED_{50} and ED_{95} (and 95% confidence intervals) of eltanolone for induction of anesthesia in healthy lorazepam-premedicated patients were 0.46 (0.40–0.52) and 0.82 (0.68–1.28) $mg \cdot kg^{-1}$, respectively.

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