cause resistance to nondepolarizing agents, as these receptors do not participate in neuromuscular transmission. Thus, although our observations support the concept that resistance is associated with an increase in the total number of receptors, we suspect that the resistance phenomenon is due either to an increase in the number of junctional acetylcholine receptors, occurring pari passu with the increase in extrajunctional receptors, or to an altogether different mechanism. We are currently investigating these alternatives.

The authors gratefully acknowledge the excellent technical assistance of Ms. Valerie Burger.

REFERENCES


The Effect of Propofol on Adrenocortical Steroidogenesis: A Comparative Study with Etomidate and Thiopental

ROBERT J. FRAGEN, M.D.,* HOWARD W. WEISS, M.D.,† AGOSTINO MOLTENI, M.D., PH.D.‡

Propofol (Diprivan®) is a sterically hindered phenol with intravenous hypnotic properties. It is currently under in-

* Professor of Clinical Anesthesia.
† Resident in Anesthesia.
‡ Professor of Pathology.

Received from the Northwestern University Medical School, Department of Anesthesia, 303 E. Superior Street, Passavant Pavilion—Room 360, Chicago, Illinois 60611. Accepted for publication January 27, 1987. Work was done in the Departments of Anesthesia and Pathology, Northwestern University, Chicago, Illinois. Supported in part by a grant from Stuart Pharmaceuticals, a Division of ICI Americas, Inc. Presented at the 1986 meeting of the American Society of Anesthesiologist, Las Vegas, Nevada.

Address reprint requests to Dr. Fragen.

Key words: ACTH; stimulation. Adrenocortical hormones: aldosterone; cortisol. Anesthetics, intravenous: etomidate; propofol; thiopental.

vestigation in the United States as an anesthetic induction agent. A large volume of distribution and short elimination half-life give propofol potential advantages for induction of anesthesia in outpatients and as a maintenance hypnotic agent by iv infusion or multiple injection.1,2 The effects of induction doses of propofol on steroidogenesis are unknown.

Etomidate inhibits adrenal steroidogenesis by a concentration-dependent block of both cholesterol side chain cleavage enzyme and 11-β-hydroxylase.3–5 This occurs with doses as low as the recommended induction dose of etomidate, 0.3 mg/kg.6,7 Prolonged intravenous infusions of etomidate, given for sedation in intensive care units to multiple trauma patients not receiving steroids, were associated with low plasma cortisol concentrations and increased mortality due to infection.6,7 Induction doses of thiopental do not suppress the adrenal cortex.4
TABLE 1. Demographic Data for Patients Undergoing Arthroscopic Procedures (x ± SD)

<table>
<thead>
<tr>
<th></th>
<th>Propofol</th>
<th>Etomidate</th>
<th>Thiopental</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>32 ± 5</td>
<td>40 ± 14</td>
<td>36 ± 13</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>157 ± 4</td>
<td>152 ± 5</td>
<td>156 ± 7</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>91 ± 8</td>
<td>78 ± 17</td>
<td>91 ± 20</td>
</tr>
<tr>
<td>Anesthetic Time (h)</td>
<td>1.3 ± 0.3</td>
<td>1.4 ± 0.5</td>
<td>1.3 ± 0.2</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>10/0</td>
<td>9/1</td>
<td>9/1</td>
</tr>
</tbody>
</table>

There were no significant differences between the drug groups.

The purpose of this study was to evaluate propofol's effect on adrenal steroidogenesis after single intravenous induction doses, and to compare this effect with that produced by induction doses of etomidate or thiopental.

**Materials and Methods**

Thirty healthy patients (ASA physical status I or II), age 18–65 yr, who were scheduled for arthroscopic surgery performed in the morning, gave written informed consent to participate in this institutionally approved study. Excluded were females who were pregnant, nursing, or of child-bearing potential; anyone with a known endocrine abnormality, previous adverse experience associated with general anesthesia, or allergy to any of the study drugs; and anyone chronically or acutely taking steroids.

The patients were randomly assigned to have anesthesia induced with either propofol 2.5 mg/kg (n = 10, group 1), etomidate 0.3 mg/kg (n = 10, group 2), or thiopental 4 mg/kg (n = 10, group 3) administered iv over 20–30 s. All patients received fentanyl 1.5 μg/kg iv 3 min prior to anesthetic induction. Anesthesia was maintained with 1–2% inspired enflurane added to a 50:50 mixture of N₂O and O₂ administered by facemask. Ventilation was assisted to maintain end-tidal CO₂ between 35 and 40 torr.

Venous blood samples were obtained through a large bore iv at 1 min prior to, and 30, 60, 90, 120, 150, 180, and 210 min after, induction of anesthesia. The plasma was separated and frozen for later determination of cortisol (Gamma coat®[125I] Cortisol RIA Kit, Clinical Assays, Travenol Laboratories, Inc.), aldosterone (Count-a-coat® no extraction aldosterone kit, Diagnostic Products Corporation), and ACTH (Immunonuclear Corporation) by radioimmunoassay. At 150 min post-induction, cortrosyn 0.25 mg (ACTH stimulation test) was given iv.

All results except ACTH concentrations are expressed as mean ± SD. ACTH results are expressed as median, because some ACTH concentrations were expressed as either <25 or >500, and were not specific numbers. Hormone concentrations were analyzed with a two-way ANOVA with repeat measures. Post-hoc testing for within-group comparisons of plasma hormone concentrations were analyzed with the paired t-test with Bonferroni corrections. Between-group comparisons were made with the unpaired t-test with Bonferroni corrections. ACTH concentrations were evaluated using the Wilcoxon two-sample test and the Kruskal-Wallis test. The null hypothesis was rejected when P < 0.05.

**Results**

The three groups participating in this study were similar with respect to age, height, weight, sex distribution, and anesthesia time (table 1).

The mean control cortisol concentrations before induction and the mean ± SD cortisol concentrations after each anesthetic induction agent are shown in figure 1. Control concentrations (ng/ml) in all three groups decreased significantly during the first 30 min after induction of anesthesia (17 ± 6 to 12 ± 5 after propofol, 18 ± 5 to 12 ± 4 after etomidate, and 19 ± 7 to 12 ± 4 after thiopental). Following etomidate, cortisol concentrations from 30 min through 180 min after anesthetic induction remained significantly lower than control values (range = 12 ± 4 to 10 ± 4). The groups receiving propofol or thiopental had rising cortisol concentrations after surgery, but these were significantly higher than control values only after ACTH stimulation, except for patients receiving propofol at the 90-min mark. There were significant differences in cortisol concentrations between the etomidate group, and both the thiopental and propofol groups, from 90 min post-induction until the end of the experiment. There were no significant differences in cortisol concentrations between the thiopental and propofol groups at any time.

![Fig. 1. Blood cortisol concentrations before and after induction of anesthesia with thiopental, propofol, or etomidate groups. ACTH was administered 150 min after induction. * = Significant difference (P < 0.05) between blood cortisol concentrations after etomidate and those after either thiopental or propofol at the same time.](http://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=/data/journals/jasa/931386/...03/30/2017)
The mean control aldosterone concentrations before induction, and the mean ± SD aldosterone concentrations after each anesthetic induction agent, are shown in figure 2. Aldosterone concentrations (ng/ml) decreased significantly from control values in the patients receiving etomidate (93 ± 53 to 57 ± 28) 30 min after induction of anesthesia, and remained low until the end of the experiment (range = 55 ± 30 to 43 ± 16). Both the propofol and thiopental groups had rising post-induction aldosterone concentrations. These concentrations after propofol were significantly above the control value of 101 ± 56 at all sampling times (range = 280 ± 151 to 190 ± 67). After thiopental, the concentrations of aldosterone were significantly higher than the control values of 88 ± 39 at all sampling times from 90 min and later (range = 316 ± 178 to 257 ± 176). Differences in aldosterone concentrations between the thiopental and etomidate groups were significant from 90 min after anesthetic induction until the end of the experiment. Concentrations of aldosterone after propofol were significantly different from those after etomidate at all sampling times after induction of anesthesia. At no time were aldosterone concentrations between thiopental and propofol groups significantly different.

ACTH concentrations, pg/ml (fig. 3), rose significantly after cortrosyn injection in all three groups, but otherwise remained within the normal range. The high ACTH level after cortrosyn injection reflects the cross-reactivity of the antisera used in the radioimmunoassay with cortrosyn. There were no significant between-group differences with regard to ACTH concentrations at any sampling time.

Side effects which occurred in more than one patient were headache 3/10 and nausea 2/10 after propofol; headache 4/10 and nausea 3/10 after thiopental; hypertonic or myoclonic movements on induction 3/10, and pain on injection 2/10 after etomidate. All side effects were transient and required no treatment.

DISCUSSION

This study shows that the in vivo production of cortisol and aldosterone is suppressed by anesthetic induction doses of etomidate, but not by induction doses of either thiopental or propofol. Cortisol and aldosterone concentrations increased similarly in response to the stress of surgery and the ACTH stimulation test after propofol and thiopental. The absence of this response after ACTH stimulation in the patients receiving etomidate suggests an inhibition of adrenocortical hormone production at the level of the adrenal cortex. This is consistent with the findings of previous authors.4,5

In an editorial in ANESTHESIOLOGY,6 discussing the adrenocortical suppressive effects of etomidate, the question was asked, "Do these changes occur in men as well as women?" The two articles to which the editorial referred4,5 reported studies only involving female patients. Nine of ten patients receiving etomidate in this study were males; thus demonstrating that etomidate-induced adrenocortical suppression occurs in males as well.

The decrease in cortisol concentrations seen in all three groups at 30 min post-induction is most likely due to general anesthesia with a possible contribution from diurnal variation. Baseline cortisol concentrations normally peak between 7:00 and 8:00 AM at 9–25 μg/100 ml, and then decline to a trough of 3–12 μg/100 ml by 4:00 PM. All anesthetic inductions in this study began between 7:30 and 9:30 AM. Cortisol concentrations would be declining.

FIG. 2. Blood aldosterone concentration before and after induction of anesthesia with thiopental, propofol, or etomidate. * = Significant difference (P < 0.05) between blood aldosterone concentrations after etomidate and those after thiopental or propofol at the same time. † = Significant difference (P < 0.05) between blood cortisol concentrations after etomidate and those after propofol at the same time.

FIG. 3. Blood ACTH concentrations before and after induction of anesthesia with thiopental, propofol, or etomidate. ACTH (cortrosyn 0.25 mg iv) was administered 150 min after induction. There were no differences between the groups.
at these induction times. Because all operations began at essentially the same time of day, diurnal variation could not have contributed to the differences between groups 30 min after induction and later.

The data derived in this investigation were suggested from in vitro studies by Kenyon et al.,9 Lambert et al.,10 and Robertson et al.,11 who found that the concentration of etomidate required to suppress adrenocortical steroidsogenesis is obtained following typical clinical doses. The concentrations of thiopental and propofol required to achieve adrenocortical suppression were greater than those produced clinically.

The side effects seen after propofol induction were similar to those seen after thiopental induction; they did not include the myoclonic movements or pain seen after etomidate injection.

In conclusion, the ability of the adrenal cortex to secrete cortisol and aldosterone in response to surgical stress or ACTH stimulation was not blocked after 2.5 mg/kg of propofol iv. Larger doses of propofol might have a different effect, but they were not studied. Therefore, induction doses of propofol have a similar non-suppressive adrenocortical effect as induction doses of thiopental, and are different than the adrenocortical suppressive effect of induction doses of etomidate.

The authors wish to acknowledge George Speck for providing the hormonal measurements and Connie Mora for her assistance in the preparation of the manuscript.

Anesthesiology

Unequal Effects of Cardiopulmonary Bypass-induced Hypothermia on Neuromuscular Blockade from Constant Infusion of Alcuronium, d-Tubocurarine, Pancuronium, and Vecuronium

W. BUZELLO, M.D.,* D. SCHLUERMANN, M.D.,† T. POLLMAECHER, M.D.,‡ G. SPIELNER§

Recent publications suggest that hypothermia may either attenuate or enhance nondepolarizing neuromuscular blockade, depending on the specific muscle relaxant involved.1–4 However, within these studies, the possible significance of organ bath cooling versus hypothermic cardiopulmonary bypass is difficult to ascertain. We, therefore, examined the neuromuscular blockade induced by four nondepolarizing muscle relaxants for its response to cardiopulmonary bypass-induced hypothermia in the clinical setting.

MATERIALS AND METHODS

Forty patients, ASA Physical Status III and IV, undergoing coronary artery bypass grafting or aortic or mitral valve replacement gave informed consent to participate