Postoperative adrenocortical function was compared in 23 outpatients receiving either thiopental, 4 mg/kg, for induction and a thiopental infusion, 0.26 mg·kg⁻¹·min⁻¹, in combination with nitrous oxide 70% for maintenance of anesthesia (control); etomidate, 0.4 mg/kg, for induction followed by an etomidate infusion, 0.02 mg·kg⁻¹·min⁻¹, and nitrous oxide 70% for maintenance (etomidate I); or etomidate, 0.4 mg/kg, for induction and a thiopental infusion, 0.22 mg·kg⁻¹·min⁻¹, in combination with nitrous oxide 70% for maintenance (etomidate II). The norepinephrine response to anesthesia and surgery did not differ significantly between the three groups. The postoperative cortisol response to ACTH stimulation was normal in the control group (maximum rise in plasma cortisol was 20.1 ± 2.9 µg/dl [mean ± SEM]), however, it was decreased in all patients receiving etomidate, whether by a short infusion (mean change in plasma cortisol was −3.8 ± 1.9 µg/dl) or as a single induction dose (mean change in plasma cortisol was −4.0 ± 2.0 µg/dl). Similarly, the postoperative aldosterone levels in the control group increased normally in response to ACTH (+10.2 ± 3.0 ng/dl) but decreased in both the etomidate I and etomidate II groups (−3.0 ± 0.7 ng/dl and −3.9 ± 1.0 ng/dl, respectively). Because ACTH was administered exogenously, etomidate-induced suppression of adrenocortical response appeared to be a direct effect on the adrenal gland, which was present at a time when the serum etomidate levels were in the subhypnotic range. Anesthetists using etomidate should be aware that biochemical adrenocortical suppression may follow even a single induction dose of this drug. Furthermore, adrenal steroid supplementation may be required if patients receiving etomidate develop an unexpected stress during the early postoperative period.

Key words: Anesthetics, intravenous; etomidate; thiopental. Anesthetic techniques: continuous infusion. Hormones: ACTH; aldosterone; cortisol. Sympathetic nervous system: catecholamines, norepinephrine.

ETOMIDATE (Amidate®) is an intravenous anesthetic that has been used for induction and maintenance of anesthesia as well as for prolonged sedation of critically ill patients. Its use is associated with a rapid onset and recovery,1 excellent cardiovascular stability,2 and the absence of histamine release.3 Recently, investigators in England reported an increased mortality rate associated with low plasma cortisol levels in patients receiving prolonged sedation with etomidate.1-4 We have demonstrated that etomidate inhibits adrenal steroidogenesis by producing a concentration-dependent block of both cholesterol side-chain cleavage enzyme and 11-β-hydroxylase.7

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Important questions relating to the effect of etomidate on adrenocortical reserve after a short intraoperative infusion or a single induction dose remain unanswered. To date there have been no controlled studies comparing the hormonal effects of etomidate with other standard induction agents (e.g., thiopental). Since plasma cortisol and aldosterone levels vary widely during the perioperative period, it is unclear that decreased levels of these hormones are associated uniquely with the use of etomidate rather than a nonspecific effect of multiple drug therapy or the existing clinical situation (e.g., underlying disease state, sedation, anesthesia). Moreover, no prior data exists with regard to the adrenal response to ACTH stimulation in the perioperative setting. Using a randomized, controlled study design, we evaluated postoperative adrenocortical function following either a single induction dose or a short infusion of etomidate (versus thiopental) in healthy outpatients.

Materials and Methods

Twenty-three healthy (ASA physical status I), unpremedicated women presenting for elective midtrimester abortions or cervical biopsies were studied according to a protocol approved by the local institution review board. After obtaining informed consent, patients were assigned randomly to one of three treatment groups: control (thiopental for induction and maintenance, n = 8), etomidate I (etomidate for induction and maintenance, n = 7), or etomidate II (etomidate for induction only, n = 8).

Patients were monitored with an electrocardiogram, Dinamap® blood pressure cuff, and precordial stethoscope. All patients received droperidol, 0.5 mg, and either fentanyl, 1.5 µg/kg, or meperidine, 1 mg/kg, intravenously, immediately prior to induction of anesthesia. Anesthesia was induced with thiopental, 4 mg/kg (control) or etomidate, 0.4 mg/kg (etomidate I and II), and when the patient became unresponsive (i.e., loss of response to commands, loss of eyelid reflex), nitrous oxide 70% in oxygen (7:3 l/min) was administered via a tight-fitting mask using a conventional circle absorber system. Inspired oxygen concentration was measured using a calibrated oxygen alarm monitor. To supplement nitrous oxide, patients in the control and etomidate II groups received an infusion of thiopental (4 mg/ml) at an average maintenance infusion rate of 17.6 and 14.1 mg/min, respectively; whereas, patients in the etomidate I group received an infusion of etomidate (0.4 mg/ml) at an average maintenance infusion rate of 1.6 mg/
min. During the maintenance period, end-tidal carbon dioxide (CO₂) and forehead electromyography (EMG) were monitored using a Datex® anesthesia activity monitor (Puritan-Bennett Corporation). An attempt was made to maintain a stable level of anesthesia in all groups (e.g., constant respiratory rate, heart rate and blood pressure, stable end-tidal CO₂ and EMG, and the absence of purposeful movement) by altering the rate of the infusion in response to clinical signs of inadequate anesthesia or excessive drug effect. The infusion was discontinued when surgical stimulation ceased, and the nitrous oxide was discontinued 1–2 min later.

Time to awakening was defined as the time from discontinuation of the nitrous oxide until the patient was able to respond to simple commands. The orientation time was the time from discontinuation of nitrous oxide until the patient was oriented to person and place. The duration of anesthesia was considered the time from administration of the intravenous induction dose of thiopental or etomidate until discontinuation of nitrous oxide.

Blood samples were drawn from an indwelling venous catheter. Plasma cortisol and norepinephrine levels were measured 15–30 min before induction of anesthesia, intraoperatively at the time of maximum surgical stimulation, and postoperatively at the time of the ACTH stimulation test. Cortisol analyses were performed using a highly specific radioimmunoassay⁸ after purification over a celite column (Endocrine Metabolic Center, Oakland, California).⁹ Normal cortisol levels are 5–25 μg/dl and an increase of at least 7 μg/dl above the basal cortisol level at 60 min is considered a normal response to ACTH.¹⁰ Aldosterone also was measured by a specific radioimmunoassay (Endocrine Sciences Laboratory, Tarzana, California).¹¹ Normal aldosterone values are 3–16 ng/dl and a normal increase in aldosterone following ACTH stimulation ranges from 7 to 33 ng/dl. Norepinephrine analyses were performed by an HPLC method using amperometric detection.¹² The norepinephrine assay was sensitive to 10 pg/ml, with a coefficient of variation of ±5%. Plasma etomidate levels were determined postoperatively at the time of the ACTH stimulation test using a modification of a high-performance liquid chromatography (HPLC) method.¹³ The etomidate standard curve was linear over a concentration range of 5–500 ng/ml, with a coefficient of variation of ±7%.

The ACTH stimulation test was performed approximately 30 min after the patient arrived in the recovery room. After collecting plasma norepinephrine, cortisol, aldosterone, and etomidate samples, synthetic ¹²⁴ACTH (Cortrosyn®, Organon, West Orange, New Jersey), 250 μg, was injected intravenously. Plasma samples for cortisol determinations were obtained 30 and 60 min after the ACTH injection. Samples for plasma aldosterone analysis were obtained at time zero and 60 min after ACTH stimulation from four patients in each group. Postural changes in blood pressure and heart rate were assessed after completion of the ACTH stimulation test (at the time of discharge from the recovery room).

**Data Analysis**

Means and variances were determined for each of the three study groups with respect to entry characteristics, preoperative, intraoperative, and postoperative variables (including cortisol and norepinephrine levels), as well as changes in cortisol and aldosterone levels with ACTH stimulation. In addition, these data were analyzed with the Kruskal-Wallis statistic¹⁴ (a standard nonparametric test for multiple groups) and where a significant difference was found, the Mann-Whitney Rank Sum test was performed. In all cases, the Bonferroni inequality was used to correct for multiple comparisons, using an overall α-error of <0.05. Temporal changes in cortisol and norepinephrine levels were evaluated using repeated measures of analysis of variance, with P < 0.05 considered significant.

**Results**

There were no significant differences among the three patient groups with respect to age, weight, types of procedure (or gestational age), duration of anesthesia, or time elapsed from induction (or the end of surgery) to the beginning of the ACTH stimulation test (table 1, all P values > 0.05). Preoperative, intraoperative and postoperative cortisol and norepinephrine values are summarized in table 2. There were no statistically significant temporal changes in the cortisol levels, while the norepinephrine levels were increased nonsignificantly with surgical stimulation in all three groups. No significant differences in these “stress” hormone levels existed between the three study groups preoperatively, intraoperatively, or in the early postoperative period (all P values > 0.05). At the time of discharge from the recovery room, no postural changes in blood pressure or heart rate were present.

Plasma cortisol levels prior to ACTH stimulation (approximately 1 h after induction of anesthesia with either etomidate or thiopental) showed wide variation, with a trend towards higher levels in the control group. The thiopental (Control) group increased 20.1 ± 2.9 μg/dl (mean ± SEM) in response to ACTH stimulation, whereas cortisol responses to ACTH stimulation were blunted in both etomidate groups. Moreover, the effect of etomidate on adrenal responsiveness was equally apparent with an induction dose followed by a short
ETOMIDATE VS. THIOPENTAL AND ADRENAL FUNCTION

TABLE 1. Demographic Characteristics of the Three Treatment Groups Receiving either Thiopental (Control), Etomidate (Etomidate I), or a Combination of Etomidate and Thiopental (Etomidate II) as Adjuvants to Nitrous Oxide.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>Etomidate I</th>
<th>Etomidate II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>8</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>21.0 ± 7.3</td>
<td>24.1 ± 6.9</td>
<td>27.5 ± 6.7</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>67.2 ± 13.5</td>
<td>65.7 ± 11.7</td>
<td>64.1 ± 14.0</td>
</tr>
<tr>
<td>Type of procedure (abortion/biopsy)</td>
<td>7/1</td>
<td>6/1</td>
<td>7/1</td>
</tr>
<tr>
<td>Opiate analgesic (fentanyl/meperidine)</td>
<td>6/2</td>
<td>2/5</td>
<td>5/3</td>
</tr>
<tr>
<td>Induction dose (mg)</td>
<td>256 ± 44</td>
<td>26.0 ± 4.3</td>
<td>25.2 ± 5.8</td>
</tr>
<tr>
<td>Maintenance dose (mg)</td>
<td>407 ± 172</td>
<td>—</td>
<td>289 ± 50</td>
</tr>
<tr>
<td>Thiopental</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Etomidate</td>
<td>—</td>
<td>30.6 ± 12.7</td>
<td>—</td>
</tr>
<tr>
<td>Duration of infusion (min)</td>
<td>23.1 ± 10.4</td>
<td>19.7 ± 8.4</td>
<td>20.5 ± 9.6</td>
</tr>
<tr>
<td>Duration of anesthesia†</td>
<td>24.8 ± 10.6</td>
<td>22.3 ± 8.4</td>
<td>25.0 ± 9.3</td>
</tr>
<tr>
<td>Awakening time (min)</td>
<td>9.2 ± 4.6</td>
<td>4.7 ± 2.9</td>
<td>5.8 ± 2.3</td>
</tr>
<tr>
<td>Orientation time (min)</td>
<td>9.9 ± 4.7</td>
<td>5.5 ± 3.1</td>
<td>6.4 ± 2.7</td>
</tr>
<tr>
<td>ACTH stimulation test‡</td>
<td>62.0 ± 20.8</td>
<td>52.7 ± 8.7</td>
<td>48.2 ± 19.6</td>
</tr>
</tbody>
</table>

* Mean values ± SD (or number of patients).
† Time from initial injection of thiopental or etomidate until nitrous oxide was discontinued (min).
‡ Time from induction of anesthesia until start of the ACTH stimulation test (min).

maintenance infusion of etomidate (mean decrease in plasma cortisol equal to 3.8 ± 1.9 μg/dl) as with a single bolus dose of etomidate for induction (mean decrease in plasma cortisol equal to 4.0 ± 2.0 μg/dl).

Not only was the mean response among the etomidate groups different than the mean response of the thiopental controls, but the difference in response was apparent for every patient in the study (fig. 1). All patients receiving etomidate had abnormal responses to ACTH stimulation, while all patients receiving thiopental had normal responses (P < 0.001). Similarly, aldosterone levels (fig. 2) showed a normal response to ACTH in the control group (a mean increase of 10.2 ± 3.0 ng/dl) but a blunted response in both etomidate groups (mean decreases of 3.0 ± 0.7 ng/dl and 3.3 ± 0.9 ng/dl, respectively). When each of the three study groups was reanalyzed according to the type of opiate analgesic administered prior to induction (i.e., fentanyl or meperidine), no differences were found in cortisol or aldosterone responses to ACTH stimulation. At the time of the ACTH stimulation test, plasma etomidate levels were 174–265 ng/ml and 31–66 ng/ml for the etomidate I and etomidate II groups, respectively.

Discussion

Etomidate has been used in Europe for more than 10 years, yet the first report of an effect on plasma cortisol appeared in 1982.15 This was followed by a series of reports of increased mortality associated with low plasma cortisol levels in patients receiving prolonged infusions of etomidate for sedation.4–6 Additional anecdotal reports have confirmed an association between administration of etomidate and decreased plasma cortisol levels.16,17

Release of ACTH from the pituitary gland in response to stress is the principal stimulus to cortisol production by the adrenal cortex and also increases aldosterone production. Cortisol production may be decreased either because the pituitary is not releasing ACTH or because the adrenal cortex is not responding to a normal ACTH stimulus. The ACTH stimulation test is a standard screening test that can be used to distinguish between a central (i.e., pituitary) and peripheral (i.e., adrenal gland) mechanism for decreased circulating plasma cortisol and aldosterone levels. By providing exogenous ACTH, the state of pituitary function becomes irrelevant, and ad-

TABLE 2. Effects of Surgery and Anesthesia on Cortisol (μg/dl), and Norepinephrine (pg/ml) Levels in Outpatients*¹

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Preoperative</th>
<th>Intraoperative</th>
<th>Postoperative</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cortisol</td>
<td>Norepinephrine</td>
<td>Cortisol</td>
</tr>
<tr>
<td>Control</td>
<td>35.0 ± 19.2</td>
<td>86 ± 57</td>
<td>26.2 ± 9.2</td>
</tr>
<tr>
<td>Etomidate I</td>
<td>27.2 ± 11.4</td>
<td>76 ± 50</td>
<td>21.2 ± 11.3</td>
</tr>
<tr>
<td>Etomidate II</td>
<td>27.7 ± 8.2</td>
<td>90 ± 50</td>
<td>27.3 ± 16.5</td>
</tr>
</tbody>
</table>

* Mean values ± SD.
Fig. 1. Serum cortisol levels before (PRE) and 60 min after (POST) administration of synthetic \( ^{1-24} \text{ACTH} \) in patients receiving either thiopental for induction and maintenance (control), etomidate for induction and maintenance (etomidate I), or etomidate for induction only (etomidate II).

Steroidogenesis by blocking two mitochondrial cytochrome P-450 dependent enzymes in the steroidogenic pathway, namely cholesterol side-chain cleavage enzyme and 11- \( \beta \)-hydroxylase.\(^7\) In that report, the presence of an enzymatic block of 11- \( \beta \)-hydroxylase (which converts 11-deoxycorticisol to cortisol) was demonstrated in a patient receiving a prolonged infusion of etomidate. Abnormally high levels of 11-deoxycorticisol were measured after the infusion was discontinued, with the 11-deoxycorticisol: cortisol ratio increasing from 0.02 to 10.

In this study, we have demonstrated that patients receiving etomidate during surgery have a blunted adrenocortical response to ACTH stimulation postoperatively compared with a control group receiving thiopental (figs. 1 and 2), even though the intraoperative anesthetic conditions and hormone levels were similar (tables 1 and 2). This effect of etomidate was present both in patients receiving an induction dose followed by a short maintenance infusion of etomidate as well as in those receiving only a single dose for induction. Furthermore, the effect was apparent at a time when the plasma etomidate levels were in the subhypnotic concentration range.\(^18,19\)

Measurement of cortisol concentrations at the end of surgery and in the early postoperative period in this and other studies\(^17,20\) revealed no significant differences, irrespective of whether etomidate or thiopental was used for induction of anesthesia. However, adrenocortical function might be suppressed as a result of inhibition of adrenal steroidogenesis, and yet plasma cortisol might remain relatively unchanged because its half-life is 60–90 min.\(^21\) The ACTH stimulation test therefore may be a more appropriate tool for studying the effects of etomidate on adrenocortical function. In our study, plasma cortisol levels prior to ACTH stimulation did not differ significantly between the etomidate-treated and control groups because of the wide individual variability. On the other hand, there was a clear difference in response to ACTH stimulation.

Questions relating to the time course and clinical significance of etomidate-induced adrenocortical suppression remain to be answered. While it is widely accepted that patients with Addison's disease need glucocorticoid supplementation,\(^21\) it is less clear that patients who develop transient adrenocortical suppression are at increased risk of morbidity during the perioperative period. However, reports of increased morbidity in patients receiving prolonged infusions of etomidate\(^8\) and a case report of hypotension responding to glucocorticoid therapy in an etomidate-treated patient\(^17\) are of obvious concern.

Suppression of the hormonal response to stress is a goal of so-called "stress-free" anesthesia.\(^22\) Indeed, Kehlet has proposed that the endocrine–metabolic response after surgical stress may result in increased postoperative morbidity due to the stress-induced catabolic state and

Fig. 2. Serum aldosterone levels before (Pre) and 60 min after (Post) administration of synthetic \( ^{1-24} \text{ACTH} \) in patients receiving either thiopental for induction and maintenance (control), etomidate for induction and maintenance (etomidate I), or etomidate for induction only (etomidate II).
the resultant increased demands on various body organs.\textsuperscript{23} The decrease in plasma cortisol levels associated with the use of many general\textsuperscript{24} or regional\textsuperscript{22,25} anesthetic techniques is presumably mediated by a decrease in circulating plasma ACTH levels secondary to depression of the central nervous system (CNS).\textsuperscript{2} In contrast, the mechanism by which etomidate produces a "stress-free" state relates, at least in part, to its direct effects on the adrenal cortex. Furthermore, the reports of increased mortality associated with etomidate imply that one carefully should assess the risks and benefits of achieving a state in which the ability of the organism to respond to unexpected stress (e.g., sudden postoperative hemorrhage) is altered pharmacologically.

Nevertheless, given the information currently available we would question the recommendation that etomidate should no longer be used in anesthesia.\textsuperscript{26} Clearly, those patients receiving etomidate during anesthesia who experience an untoward event during the postoperative period (requiring a rapid increase in cortisol and aldosterone production) may be at risk of increased morbidity. Based on the available information, etomidate-treated patients developing unexpected stress during the early postoperative period probably, should receive gluocorticoid and mineralocorticoid supplementation. The major advantage of etomidate over available intravenous induction agents (e.g., thiopental, ketamine) relates to the remarkable cardiovascular stability associated with its use in patients with cardiac disease.\textsuperscript{27,28} Until the clinical relevance of the adrenal suppression effects of etomidate is known, its use probably should be restricted to those situations where it offers a clinical advantage over other available drugs.

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References