The authors describe etomidate, a new intravenous nonbarbiturate hypnotic for induction of anesthesia, through a series of three separate studies undertaken at their medical facility. The results of their studies coincide with the experience of other researchers, showing etomidate to be a useful agent for induction because of its rapid onset, short duration of action, and minimal cardiovascular effects.

Prior to 1960, intravenous anesthesia was almost synonymous with the use of ultrashort-acting barbiturates. Since then, attention has been directed toward the development of nonbarbiturate compounds. Pursuit of this objective in research has resulted in the introduction of compounds representing new chemical classes into anesthetic practice: diazepam, a benzodiazepine; droperidol, a butyrophenone; fentanyl, a piperidine; ketamine, a phencyclidine; propanidid, a derivative of eugenol; and alphadione (alphaxalone and alphadolone), a steroid combination. (The latter two are not available in the United States.)

All of these compounds are valuable contributions to the practice of anesthesia, but none is a "complete" anesthetic. The search for improvements over the barbiturates therefore continues. In particular, there is a need for a hypnotic agent that induces sleep rapidly and comfortably without the problems associated with barbiturates.

In 1971, Janssen and associates reported on etomidate, a member of a new chemical class, the carboxylated imidazoles.1 In this and subsequent pharmacological studies of several animal species, etomidate was found to be "a potent, manageable and safe hypnotic of short duration of action."2 Extensive clinical studies by Doenicke and associates have confirmed that, in man, etomidate is an effective intravenous hypnotic with no analgesic properties, and with little or no effect on the cardiovascular system.3

This article will describe the pharmacology of etomidate, present our clinical experience in relation to that of other practitioners, and discuss a recommended method of use for etomidate.

Pharmacological profile

Etomidate, (R)-(+)-ethyl-l-(l-phenylethyl)-lH-imidazole-5-carboxylate, is a water soluble compound provided as the base solution, 2mg/ml in 35% propylene glycol (pH 5.0). The chemical structure is shown in Figure 1. Etomidate can cause loss of consciousness in one arm-brain circulation time.4 Compared with the rapid-acting barbiturates, the compound has a very wide margin of safety.2

In rats, the therapeutic ratio (LD₅₀/ED₅₀) is 26.0 compared with 4.6 for thiopental and 9.5 for methohexital. On a mg/mg basis, it is about 25 times more potent than thiopental and about 6 times
more potent than methohexital. The usual dosage recommended to produce sleep in adults is 20-30 mg. Duration of hypnosis is dose-dependent, usually 3-5 min. with single doses of 0.2-0.3 mg/kg. No tolerance is observed with repeated administration.

Metabolism. Unlike the barbiturates, etomidate does not follow a pattern of prolonged redistribution in the tissues. The compound is rapidly metabolized in the liver by ester hydrolysis. Plasma levels of unchanged etomidate decrease rapidly during the first 30 min. after injection and thereafter more slowly, with a half-life of 40 min. Approximately 75% of the dose is excreted in the urine during the first day after injection. The main metabolite is the carboxylic acid derivative, which is pharmacologically inactive.

Cardiovascular effects. Results of extensive studies indicate that etomidate has minimal effects on the cardiovascular system. In patients with normal circulatory systems undergoing light anesthesia with controlled respiration, etomidate produced only slight hemodynamic effects. In patients given etomidate as an induction agent, the only notable change in cardiovascular parameters was a slight increase in heart rate.

Etomidate used as an induction agent in patients with myocardial disease undergoing cardiac surgery produced a small negative inotropic effect. On the basis that this effect was less than that reported for thiopental, methohexital, propanidid and alphadione, the investigators concluded that etomidate is of value for induction of anesthesia in cardiac patients.

In a study with patients undergoing mitral valve replacement, the investigators found that the cardiovascular effects of etomidate would offer particular advantages over other intravenous agents in coronary risk patients. Confirming the hemodynamic stability seen with etomidate in high risk cardiac patients, another group of investigators concluded that etomidate would be expected to provide a greater margin of safety than the ultra-short-acting barbiturates.

Induction of anesthesia with etomidate is characteristically associated with a slight, transient fall in total peripheral resistance and mild reflex tachycardia, with no effect on coronary perfusion pressure or myocardial oxygen demand. In general, induction is remarkably smooth, and any cardiovascular effects tend to be fewer and of briefer duration than those associated with thiopental, methohexital, alphadione or propanidid.

Respiratory effects. Results of studies of both volunteers and patients have shown that etomidate has minimal effects on blood gases and respiratory function. A brief period of breath-holding may occur during induction, but reports on the incidence of apnea vary widely.

One group of investigators observed a higher incidence of apnea in association with non-narcotic, as opposed to narcotic, premedication; they suggested that this difference might have been the result of the more frequent appearance of involuntary movements (see Central Nervous System Effects), with consequent breath holding in association with non-narcotic premedication. Generally, however, the incidence of hypoventilation or apnea is reported to be less with etomidate than with thiopental, methohexital or alphadione. Spontaneous respiration returns quickly.

Central nervous system effects. Etomidate is a pure hypnotic with no analgesic effect. Changes in EEG readings after administration of an intravenous dosage of 0.3 mg/kg resemble the classic stages observed with barbiturates and other anesthetics. Unlike the barbiturates, etomidate reduces subcortical inhibition at the onset of hypnosis while inducing neocortical sleep. It has only a slight effect on the centers regulating respiratory and circulatory function. Consequently, involuntary movements (myocloni) resembling the twitches or sudden jerks seen during light natural sleep may occur during the transition to hypnosis, before sleep is deep enough to affect the subcortical structures.

These movements consist of uncontrolled, uncoordinated spontaneous contractions of individual or groups of skeletal muscles. They primarily involve the muscles of the extremities, may last for less than a minute, and are self-limiting, without residual effects. In normal subjects, these motor symptoms were reduced by diazepam, given 5-10 minutes before etomidate, and eliminated with the additional administration of fentanyl. Etomidate has no convulsant or epileptogenic activity; in fact...
it has been used without any problems in several patients with epilepsy.\(^{18}\)

**Histamine release.** On the basis of plasma histamine, blood pressure and heart rate determinations in volunteer subjects, etomidate is unlikely to cause histamine release.\(^{18}\) In the same study, both propanidid and alphadione were found to induce the release of histamine. During thiopental anesthesia there may be some hypotension, particularly in hypertensive patients partly caused by histamine release.\(^{20}\)

**Local effects.** Pain has been reported to occur at the site of etomidate injection. The incidence and severity of pain are reduced when larger veins have been used for injection as opposed to the small veins of the dorsum of the hand and the wrist. Pain may also be reduced by the combined use of narcotic analgesics and tranquilizers in premedication or by administration of a narcotic analgesic at the time of induction.

As a rule, pain is not associated with thrombophlebitis. Unlike thiopental, etomidate does not cause necrotic changes in the arteries or in skeletal muscle upon intra-arterial injection in animals.

**Clinical experience**

Initial clinical studies of etomidate in Europe and the United States were done with the sulfate form of the compound. Results were encouraging with regard to the rapidity of induction, cardiovascular and respiratory stability during induction, brevity of action, safety as demonstrated by laboratory tests, and investigators' overall favorable evaluations. However, the occurrence of venous pain and involuntary muscle movements proved an obstacle to full acceptance of etomidate by anesthesia personnel.

Therefore, in an attempt to reduce or eliminate these drawbacks while retaining the advantages of speed of action, potency and cardio-respiratory stability, a new formulation of etomidate was developed which consists of the base compound in a 35% propylene glycol solution. Studies were also carried out to determine the influence of premedication and of preinduction fentanyl on the incidence and severity of pain and movements.

We conducted three studies with etomidate. In our first study, we compared the buffered formulation of etomidate with thiopental, limiting premedication to atropine only. In the second study, we again compared etomidate with thiopental but varied the premedication with the addition of either diazepam or fentanyl. Finally, in the third study, we compared the old and new formulations of etomidate using meperidine and atropine as the premedication for all patients. Our results with the old formulation have been combined with those of other investigators reported elsewhere.\(^{21}\)

Informed consent was obtained from all patients who received etomidate in these studies, and the protocols were approved by the Human Research Committee of Montgomery Hospital.

**Study I: A randomized, controlled comparison of etomidate (sulfate compound) with thiopental**

**Patients and methods.** Twenty patients, all ASA status I and scheduled for elective surgery, were given either etomidate or thiopental for induction of anesthesia. The patients were placed into two groups of ten each. Both groups were comparable in sex, age, weight, duration of anesthesia and types of operations (Tables I and II).

Premedication was limited to atropine 0.4 mg administered intramuscularly (IM) one hour be-

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<table>
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<tr>
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<th>Patient data by induction agent (Study I)</th>
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<td><strong>Total</strong></td>
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before surgery. Etomidate 0.3 mg/kg or thiopental 5 mg/kg was administered on a randomized basis via intravenous angiocatheter. During the induction observation period, no other agents were administered except oxygen. After induction, the patients were given succinylcholine, intubated and maintained with nitrous-oxide oxygen and fentanyl at the discretion of the anesthesiologist.

During induction, onset of sleep and signs of pain on injection or involuntary movements were observed and recorded. Heart rate and blood pressure were measured between the second and third minutes after administration of the hypnotic. Within 24 hours postoperatively, sites of injection were examined for signs of local irritation, and patients were questioned as to overall acceptability of induction. In addition, blood chemistry determinations (SMA-12) were made before surgery and postoperatively on the first and usually fifth day.

Results. The ranges of induction doses were: etomidate 18-30 mg (median, 27 mg) and thiopental 300-380 mg (median, 300 mg). All patients lost consciousness within 10 sec. of drug administration, with the exception of one patient who did not sleep after 300 mg of thiopental.

During maintenance of anesthesia, all patients received fentanyl for analgesia. Median doses of fentanyl were 0.25 mg in the group given etomidate and 0.20 mg in the group given thiopental.

During the induction observation period, heart rate and blood pressure changes were minimal in both groups. No respiratory difficulties were encountered. Among the patients given etomidate, there were two instances of hypertension (changes greater than 25% as compared with preinduction values), one instance of pain on injection, and five instances of slight involuntary movements of the extremities. Among those given thiopental, there were three instances of hypertension and two instances of tachycardia (changes greater than 25% as compared with preinduction values).

Postoperatively, acceptance of anesthesia was reported as good by all patients in both groups.

No thrombophlebitis or venous irritation was observed. Nausea or vomiting occurred in five patients in the etomidate group and in seven patients in the thiopental group. Analysis of laboratory data showed no significant differences between the groups and no unusual patterns of change.

Study II: A randomized, controlled comparison of etomidate (sulfate compound) and thiopental, with premedication varied

Patients and methods. Forty-eight patients, scheduled for elective or emergency surgery, were given either etomidate or thiopental on a randomized basis. The two groups of 24 patients each were comparable in sex, age, weight, physical status, duration of anesthesia and types of operations (Tables III and IV).

To study the effect of premedication, both groups of patients were further randomly subdivided into six groups of eight patients each and received one of three premedications: atropine 0.4 mg one hour before induction, diazepam 10 mg and atropine 0.4 mg one hour before induction, or fentanyl 0.1 mg and atropine 0.4 mg 30 min before induction. All premedications were administered intramuscularly. Etomidate and thiopental were administered via angiocatheter at rates of either 30 or 60 sec. Anesthesia was maintained with nitrous oxide-oxygen, supplemented with other agents as necessary. The methods of administration and parameters evaluated were similar to those in Study I.

Table IV

<table>
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<tr>
<th>Type Operation</th>
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<td>Urological</td>
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Table III

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<th>ASA Status</th>
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<td>M</td>
<td>Median (Range)</td>
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</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etomidate</td>
<td>11</td>
<td>13</td>
<td>61 (21-93)</td>
<td>65 (50-102)</td>
</tr>
<tr>
<td>Thiopental</td>
<td>7</td>
<td>17</td>
<td>61 (26-91)</td>
<td>71 (45-113)</td>
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</table>
Results. The mean induction dosage of etomidate was 0.38 mg/kg and thiopental was 5.2 mg/kg. All patients in both groups lost consciousness rapidly, and no additional dosages of hypnotics were required for induction of anesthesia.

The cardiovascular effects were typical of those seen in our other studies. Mean values for blood pressure and heart rate at all observation points are shown in Figures 2 and 3. In the etomidate group, a transient, nonsignificant decrease in systolic blood pressure and increase in heart rate occurred at 4 min post-induction as compared with 1 min before. The only statistically significant change with etomidate was an increase in diastolic pressure at 4 min as compared with baseline \(p<0.05\).*

There was no significant difference between groups. The thiopental group had a statistically significant decrease in systolic blood pressure during the first 3 min after injection as compared with baseline and significant increase in heart rate during the first 2 min \(p<0.05\).* The blood pressure decrease was significantly greater with thiopental at 2 and 3 min after injection \(p<0.05\).**

No clinically disturbing effects were seen in either group, and no respiratory difficulties were observed.

In the etomidate group, venous pain during injection occurred in five patients, two each with diazepam and fentanyl premedication and one with atropine alone. No pain was noted in the thiopental-treated group. Pain appeared to occur more frequently and to be more severe when small veins, such as those on the dorsum of the hand, were used for injection. Rate of administration had no effect on occurrence of pain.

*Wilcoxon matched pairs signed-ranks test, two-tailed probability.
**Mann-Whitney U test, two-tailed probability.
Some involuntary movement occurred in 10 of the 24 etomidate-treated patients, four following diazepam premedication and three each following fentanyl and atropine alone. Two of these cases, both following atropine alone, were rated as moderate to severe. Involuntary movement occurred in one thiopental-treated patient following atropine alone.

Postoperatively, patient and anesthesiologist evaluations of the acceptance of induction were essentially in agreement: acceptance was considered "good" or "satisfactory" in all but one patient who had received thiopental. Phlebitis was not observed in either group. Nausea or vomiting occurred in eight patients in the etomidate group and in ten patients in the thiopental group.

**Study III: A randomized, double-blind equivalence study of two etomidate formulations**

Patients and methods. The purpose of this study was to compare the new formulation, consisting of etomidate base in a 35% propylene glycol (PPG) solution with the old formulation, consisting of etomidate sulfate in a buffered solution.

Forty-nine patients scheduled for elective surgery, one of whom underwent two procedures, were given one of the two solutions on a double-blind, randomized basis. The two groups were comparable in distribution of sex, age, weight, physical status, duration of anesthesia and types of operations (Tables V and VI).

All patients were premedicated with meperidine 1 mg/kg and atropine 0.4 mg, IM, one hour before surgery. The etomidate solutions were administered via angiocatheter over a period of up to 60 seconds, until the patient lost consciousness. Anesthesia was maintained with nitrous oxide-oxygen, supplemented as appropriate with halothane, succinylcholine, fentanyl plus droperidol, or droperidol. Again, the investigative procedure was similar to that followed in the other two studies. Blood samples were taken from selected patients on the first or second postoperative day for routine blood tests, including SMA-12.

Results. The induction dosages for both etomidate preparations were approximately 0.3 mg/kg, and they were equally effective in rapidly producing sleep.

One instance of hypotension (change greater than 25% as compared with preinduction values) occurred in each treatment group. Two instances of apnea of 5-10 sec duration occurred in each group. None of these reactions were of any clinical consequence.

In this study, any cases of involuntary movement or pain on injection were rated as either "disturbing" (clinically significant) or "nondisturbing" (minor). Involuntary movements, all
rated as nondisturbing, occurred in two patients given the buffered solution and in six given the PPG solution. Pain on injection occurred in six patients given the buffered solution, with one reaction considered disturbing, and in four patients given the PPG solution, with two reactions considered disturbing.

In nine of the ten instances of pain, the site of injection was a small vein, the exception being a case of nondisturbing pain in which the site of injection was the antecubital fossa. There was no clear relationship between the incidence of side effects and the preparation used.

Although 12 of the 49 patients* were tense or excited before anesthesia, acceptability of induction was rated postoperatively as "good" or "satisfactory" in all of the anesthesiologists' evaluations and in all but two of the patients' evaluations.

Vomiting occurred in five patients. All of these had undergone gynecological surgery, and two had received postoperative meperidine.

With one patient, some 20 min after the injection of etomidate buffered solution, the IV inadvertently infiltrated. The swelling was treated with hot wet packs and resolved within 15-20 hours. There were no other incidences of phlebitis or tissue irritation at the site of injection upon examination 24-48 hours postanesthesia.

An incidental observation made at the time of the postoperative interview was that most patients were totally amnesic for the anesthetic experience. Results of hematologic tests in nine patients and biochemical tests in two patients showed no changes from preanesthetic values beyond the usual response to surgery.

Discussion

Etomidate, a new nonbarbiturate intravenous anesthetic, may offer certain advantages over presently available induction agents. It is a pure hypnotic, highly potent on a mg/mg basis as compared with thiopental, and it has a wide safety margin. The hypnotic effect of 0.3 mg/kg etomidate compares favorably with that of 5 mg/kg thiopental and 1.5 mg/kg methohexital. The short duration of action of the drug, usually 3-5 min, with rapid recovery, is primarily due to rapid chemical breakdown by hydrolysis in the liver to pharmacologically inactive end products. Etomidate is therefore particularly suitable for outpatient surgery and short diagnostic procedures.

In spite of the short duration of action, sleep is deep and long enough to allow for adequate induction of anesthesia. The minimal cardiovascular and respiratory effects and lack of histamine release are of particular advantage in geriatric and high-risk patients and those with compromised cardiopulmonary function.

The most common side effects of etomidate are pain on injection and myoclonus. It has been reported that pain on injection is more frequent and more intense when small veins such as those in the dorsum of the hand are used rather than the large antecubital veins.18, 22, 24

Our own early observations and the results of the present studies are in agreement with these findings. Table VII shows the incidence of pain in relation to injection site. It has also been reported that the incidence of pain on injection is reduced with the new formulation25 or by premedication with diazepam or fentanyl given IM 15-45 min before induction.22

In our studies of the two formulations and the effects of premedication, the incidences of pain were too small to draw any conclusions. Premedica-

Table VI
Types of operations (Study III)

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<th>Type Operations</th>
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*50 surgical procedures

Table V
Patient data by Etomidate formulation (Study III)

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<td>PPG</td>
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<td>18</td>
<td>72 (18-94)</td>
<td>62 (48-101)</td>
<td>5</td>
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</tbody>
</table>

Table VI
Types of operations (Study III)
tion with intramuscular diazepam, fentanyl or meperidine did seem to lessen pain severity in our series, and pain did not affect overall acceptability by anesthesiologists or patients. It appears that the best way to minimize pain on injection is to use a large vein and give a narcotic analgesic such as fentanyl intravenously just before induction. When pain does occur, it is transient and generally not remembered by the patient. It has not been associated with thrombophlebitis.

The myoclonus that sometimes occurs during induction with etomidate may resemble the defensive movements seen with thiopental in the absence of analgesia. The results of our studies as well as those of others show that premedication with diazepam or a narcotic analgesic may reduce the incidence and magnitude of these movements. In our three studies, the overall incidence was 44% (8 of 18 patients) when atropine was the only premedication and 23% (15 of 66 patients) when diazepam or a narcotic analgesic was used. Involuntary movements have been reduced or completely obviated by the use of small intravenous dosages of fentanyl before induction of anesthesia.

This finding is consistent with the significant correlation reported between involuntary movements and venous pain in a retrospective review of several thousand cases. The movements are no more disturbing in many cases than the muscle contractions associated with the use of succinylcholine. They are of brief duration, are self-limiting, have no residual effects, and are not associated with epileptiform discharges on the EEG.

**Recommended method of use**

Etomidate may be preceded by any standard premedication. Approximately 1 min before induction, fentanyl 0.05-0.1 mg (1-2 ml) may be given intravenously to provide analgesia and minimize pain on injection and involuntary movement. The usual induction dose of 20-30 mg (10-15 ml) etomidate is given intravenously, to effect, over a period of 30-60 sec. It is preferable to use a large vein, such as an antecubital vein.

A slower rate of injection may be advisable in poor-risk patients. A lower induction dosage may be adequate when premedication includes a central nervous system depressant. Subsequent to initial administration, etomidate may be given again at half the initial induction dose if the patient shows signs of lightening hypnotic effect, such as swallowing or abrupt increase in heart rate or blood pressure.

Involuntary movements may occur at the time of injection or as the patient makes the transition through light sleep to full hypnosis. Such movements are self-limiting and are not inherently harmful to the welfare of the patient or disruptive to the course of anesthesia. During induction, a brief period of apnea may occur, though rarely, which can be treated in the usual manner by controlled respiration. The extensive clinical experience with etomidate involving thousands of patients has shown that it is highly unlikely that instances of apnea would require any unusual measures or interrupt normal procedures.

**Conclusion**

Etomidate is a new nonbarbiturate hypnotic which offers considerable promise as a safe and effective agent, providing smooth, pleasant induction of anesthesia. It is potent and rapid acting and has minimal cardiopulmonary effects. Therefore, while etomidate has been used for a wide variety of procedures, it may be particularly suitable for short outpatient procedures and high-risk patients. Etomidate's only apparent drawback, the possibility of pain on injection and involuntary movements, are benign and self-limiting and are minimized by following the appropriate procedure.

**REFERENCES**


