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## Etomidate as an Induction Agent in Trauma Anesthesia

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### Learning Objectives

1. To review the pharmacokinetics of etomidate
2. To describe the side effect profile of etomidate
3. To evaluate the use of etomidate in the trauma patient

Etomidate is an ultra-short-acting induction agent. It is a carboxylated imidazole-derived nonbarbiturate, nonnarcotic, hypnotic agent mainly used for induction of general anesthesia. It acts by modulating and mimicking  $\gamma$ -aminobutyric acid type A receptors. Synthesized in 1964, it was introduced as an intravenous anesthetic agent in 1972.<sup>1,2</sup>

It was hailed early as an ideal agent because of maintenance of hemodynamic stability even in patients with marked hypovolemia, minimal respiratory depression, cerebral protection, and rapid recovery. However, by the early 1980s, reports indicated that etomidate might inhibit steroid synthesis, thus increasing mortality in patients sedated with the drug for long periods in intensive care units.<sup>3,4</sup> Another study suggested that even a single induction dose might be unsafe.<sup>5</sup> Propofol became the preferred induction agent, and the use of etomidate fell dramatically in the United States.

Now, more than 30 years later, it is appropriate to reevaluate this important drug and identify means whereby the beneficial effects may be put to maximum use while adverse actions may be minimized. It is perhaps not surprising that most studies over the past 10 years have appeared in the British and Canadian literature.

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## Pharmacokinetics

The pharmacokinetics of etomidate are shown in Table 1.<sup>6</sup> The initial distribution of half-life of etomidate is 3 minutes and redistribution is 29 minutes. Elimination half-life is 2.9 to 5.3 hours. Hepatic clearance is high (18–25 ml/kg/min), as is protein binding (75%). Factors interfering with clearance include cirrhosis, increasing age, and the presence of other drugs that alter serum protein levels and affect hepatic blood flow. Metabolism is by enzyme hydrolysis, major pathways being esterification and N-dealkylation.

**Table 1. Etomidate Pharmacokinetics  
(0.3 mg/kg IV in man)**

|                                       |                  |
|---------------------------------------|------------------|
| Distribution half-life                | 2.6 ± 1.3 min    |
| Elimination half-life                 | 4.6 ± 2.6 hr     |
| Total apparent volume of distribution | 4.5 ± 2.2 l/kg   |
| Total plasma clearance                | 860 ± 230 ml/min |

Data from Van Hamme MJ, Ghoneim MM, Ambre JJ.  
Pharmacokinetics of etomidate: a new intravenous anesthetic.  
*Anesthesiology* 1978; 49:274–7.

## Systemic Effects

The minimal effects exercised by etomidate on cardiovascular function differentiate it from other commonly used agents. Comparisons of cardiac effects of both etomidate and thiopental on healthy and sick patients have repeatedly demonstrated little change with etomidate.<sup>7,8</sup> Several studies have demonstrated no myocardial depression, no effects on the conduction system, no increase in myocardial oxygen consumption, no histamine release, and limited sympathetic effects. A more recent study showed that etomidate reduced +dP/dT, cardiac output, and stroke volume and increased systemic vascular resistance. However, the decrease in systemic and coronary perfusion pressure was significantly less than with isoflurane.<sup>9</sup>

In comparison with its lack of cardiovascular effect, etomidate exerts fairly profound changes on the central nervous system (CNS). Cerebral blood flow is reduced up to 34%, cerebral metabolic rate of oxygen consumption declines 45%, and intracranial pressure (ICP) is decreased up to 50%.<sup>10</sup> In conjunction with these changes, mean arterial pressure and heart rate remained unchanged when induction and intubation were performed after etomidate-induced burst suppression was achieved in a series of 8 patients. While minimal changes in ICP were noted during induction, a marked decrease was seen in the ensuing time period.<sup>11</sup> It is important to note that normal induction doses do not predict the time for decrease of the BIS (bispectral analysis) to 5012 (i.e., appropriate time for intubation). Intracranial effects are summarized in Table 2.

Etomidate manifests a dose-dependent reversible inhibition of the 11-beta-hydroxylase enzyme that converts 11-deoxycortisol to cortisol. The block is caused by the interaction of the midazolam structure with the cytochrome P-450 system and is reversible with ascorbic acid.<sup>13,14</sup> There is

also a minor effect on the 17-alpha-hydroxylase. No large prospective study has proved the clinical, long-term significance of these changes. Several smaller studies have indicated either no adverse effects or only minimal changes, especially in ICU patients receiving steroids.<sup>15</sup> A retrospective study of 220 patients undergoing high-stress procedures compared the effect of induction doses of etomidate and sodium thiopental on indices of adrenocortical function.<sup>16</sup> Outcome and incidence of postoperative complications were identical. However, a report of the effects of single-dose etomidate on adrenocortical function in 35 critically ill patients indicated at least 24-hour suppression of function.<sup>17</sup> It seems that more controlled investigations of the effects on adrenal function are indicated, and the jury is still out.

**Table 2. Effects of Etomidate on  
Intracranial Dynamics**

- Lowers intracranial pressure
- Reduces cerebral blood flow
- Reduces cerebral metabolic rate of oxygen consumption (CMRO<sub>2</sub>)
- Maintains cerebral perfusion pressure
- Net increase in cerebral oxygen supply–demand ratio
- Maintenance of cerebral vascular reactivity
- Brain pathology reduced after acute ischemic insult in animals
- Decrease in electroencephalograph (EEG) activity. Absence of beta waves initially (as opposed to that seen with barbiturates). Association with myoclonic movements. May cause increases in epileptic EEG activity in patients with preexisting epileptic foci.

## Side Effects

Several adverse side effects of etomidate have been described<sup>18</sup> (Table 3). Pain on injection can be eliminated by injecting lidocaine intravenously immediately preceding the etomidate injection. There is no pain if central access is used. Also, the incidence of pain may be significantly decreased when an antecubital vein is used rather than a peripheral vein. Premedication with opioids or benzodiazepines and use of preinduction doses of fentanyl are other successful measures to resolve pain on injection.<sup>18</sup> Two new preparations that contain etomidate in a liquid emulsion and etomidate in hydroxypropyl-beta cyclodextrin both have low osmolarities and pH values that are more physiologic. A study in 10 volunteers revealed that, when etomidate was carried in propylene glycol, 9 of 10 subjects experienced pain.<sup>19</sup> When a lipid emulsion was used, only 1 person experienced pain. There was no relation between pain or venous sequelae and histamine release. Although etomidate was associated with an increased incidence of nausea and vomiting in earlier studies, other investigations have yielded no difference between etomidate and thiopental.<sup>7</sup>

Myoclonus after etomidate injection has been reported in 0% to 35% of cases.<sup>7,18</sup> The intensity is also highly variable.

**Table 3. Incidence of Side Effects with Intravenous Induction Agents**

|                             | Thiopental<br>(n=12) | Etomidate<br>(n=10) | Propofol<br>(n=12) | Midazolam<br>(n=10) |
|-----------------------------|----------------------|---------------------|--------------------|---------------------|
| Apnea (no.)                 | 2                    | 1                   | 7*                 | 1                   |
| Duration of apnea (min)     | 1                    | 0.5                 | 1–6                | 5                   |
| Bradypnea (no.)             | 2                    | 4                   | 2                  | 3                   |
| Duration of bradypnea (min) | 3–3.5                | 2–8                 | 5–12               | 10–30               |
| Pain (no.)                  | 1                    | 4                   | 4                  | 0                   |
| Myoclonus (no.)             | 0                    | 3                   | 0                  | 0                   |

Data are numbers of patients.

\*P<0.05 between groups.

From Canessa R, Lema G, Urzúa J, et al. Anesthesia for elective cardioversion: a comparison of four anesthetic agents. *J Cardiothorac Vasc Anesth* 1991; 5:566–8. Used with permission from Elsevier.

Frequency correlates directly with pain and inversely with premedication and speed of injection. Although the movements may be violent and random, there is no associated seizure activity on the electroencephalogram. Muscle tone is increased, as shown by electromyographic studies. It has been suggested that these movements may represent a sign of stage 2 disinhibition. Measures to decrease the incidence of myoclonic activity are outlined in Table 4.

**Table 4. Eliminating Myoclonus**

- Minimal to no incidence with 1.5 mg/kg lidocaine and 1.5 µg/kg fentanyl given intravenously immediately preceding etomidate injection
- Rapid injection of induction dose
- Use of rapid-acting muscle relaxants after etomidate injection

**Table 5. Etomidate in Trauma (0.1–0.2 mg/kg)**

- Preserves cardiovascular status
- Causes minimal respiratory depression
- Has minimal drug interaction

### Use of Etomidate in Trauma

As described above, the minimal effects of etomidate on the cardiovascular system, its beneficial effects on the CNS, and its short duration of action suggest a very useful role in anesthetic care of the trauma patient (Tables 5 and 6). A comparison of the hemodynamic response to rapid-sequence induction using rocuronium and thiopental or etomidate indicated that adverse reactions (hypertension, tachycardia, or hypotension) were attenuated more with etomidate.<sup>20</sup> However, in the absence of neuromuscular blocking agents, propofol (2 mg/kg) rather than thiopental (6 mg/kg) or etomidate (0.3 mg/kg), all combined with remifentanyl, provided adequate intubating conditions in a study of 45 patients.<sup>21</sup> Etomidate may be a better choice than ketamine because the psychomimetic effects of the latter drug may present a problem with the differential diagnosis of drug/alcohol use and postoperative delirium. Also, ketamine has a variable dose-dependent indirect sympathomimetic action that is not seen with etomidate, and it may also be a direct myocardial depressant.<sup>22</sup>

As noted previously, etomidate has little effect on intracranial pressure. A beneficial effect has been shown to extend to the patient with eye injury: little or no increase in intraocular pressure was observed with the use of etomidate.<sup>23</sup> A final unexplained effect of etomidate has been described in an arousal action seen in a comatose patient on high-dose steroids.<sup>24</sup> The authors suggest that a catatonic state induced by steroids could be reversed by a specific antagonistic effect of etomidate.

**Table 6. Duration of Action of Induction Agents**

|                        | Thiopental<br>(n=12) | Etomidate<br>(n=10) | Propofol<br>(n=12) | Midazolam<br>(n=10) |
|------------------------|----------------------|---------------------|--------------------|---------------------|
| Induction time (min)   | 31 (10–50)           | 34 (12–49)          | 17 (10–40)         | 68 (30–220)*        |
| Awakening time (min)   | 4.5 (1.3–9.9)        | 5.5 (3.2–11)        | 5.3 (2.4–18)       | 7.1 (0.6–66)†       |
| Orientation time (min) | 1.0 (0.2–2.5)        | 0.9 (0.4–2.1)       | 1.1 (0.3–2.1)      | 1.6 (0.7–10)†       |

Data are given as median (range).

\*P<0.01 between groups; †P<0.05 between groups

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## Summary

Etomidate has proven cardiovascular stability. Effects on intracranial dynamics, especially in head-injured patients, are beneficial. The side effect of myoclonus may interfere with neurologic assessment, although the complication should be short lived and can be aborted by rapid injection and use of muscle relaxants. Adverse effects on adrenocortical function, especially after a single dose, although suggested, have still not been proven conclusively.

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