

# A review of etomidate for rapid sequence intubation in the emergency department

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## ABSTRACT

Etomidate is a sedative–hypnotic chemically unrelated to other induction agents. The pharmacological and safety profile of etomidate offers many advantages for induction during rapid sequence intubation (RSI) in the emergency department (ED). Its onset of action is within 5 to 15 seconds, and its duration of action is 5 to 15 minutes. Unlike thiopental, propofol, midazolam and, to a lesser extent, ketamine, etomidate has minimal respiratory or cardiovascular effects and can be safely used in patients with hemodynamic instability or cardiac ischemia. Etomidate is cerebroprotective, with the ability to decrease intracranial pressure and maintain cerebral perfusion, making it an ideal agent for patients with head injuries. Of the currently available induction agents, etomidate offers the most favourable safety profile and is the least likely to produce adverse effects in patients with unknown or untreated medical conditions. Etomidate may cause pain on injection, myoclonic movements on induction, hiccups, nausea and vomiting. Transient adrenal suppression has been reported, but not to a clinically significant degree, after single induction doses for ED RSI. Etomidate has been well studied in the ED and should be adopted for RSI in specific ED patient groups.

**Key words:** etomidate; sedative–hypnotic; agents, induction; rapid sequence intubation; injuries, head

## RÉSUMÉ

L'étomidate est un sédatif–hypnotique dont les propriétés chimiques n'ont aucun lien avec les autres agents d'induction. Le profil pharmacologique et d'innocuité de l'étomidate offre de nombreux avantages pour l'induction lors d'une intubation à séquence rapide (ISR) à l'urgence. Son délai d'action est de 5 à 15 secondes et sa durée d'action est de 5 à 15 minutes. Contrairement au thiopental, au propofol, au midazolam et, à un degré moindre, à la kétamine, l'étomidate a très peu d'effet aux niveaux respiratoire et cardiovasculaire et peut être utilisé en toute sécurité chez des patients hémodynamiquement instables ou en ischémie cardiaque. L'étomidate a un effet cérébroprotecteur, ayant la capacité de diminuer la pression intracrânienne et de maintenir la perfusion cérébrale, ce qui en fait un agent idéal pour les victimes de traumatismes crâniens. Parmi les agents d'induction présentement disponibles, l'étomidate offre le profil de sécurité le plus favorable et est le moins susceptible de provoquer des effets indésirables chez des patients souffrant de maladies insoupçonnées ou non traitées. L'étomidate peut causer une douleur à l'injection, des mouvements myocloniques à l'induction, un hoquet, des nausées et des vomissements. On a signalé certains cas d'insuffisance surrénalienne transitoire après des doses simples d'induction pour une ISR à l'urgence, mais sans conséquences cliniques. L'étomidate a fait l'objet de nombreuses études à l'urgence et devrait être adopté pour l'ISR chez des groupes de patients spécifiques.

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Received: Jan. 7, 2002; final submission: Mar. 3, 2002; accepted: Mar. 5, 2002

*This article has been peer reviewed.*

## Introduction

Rapid sequence intubation (RSI) has become the standard technique for airway management in the emergency department (ED). Administration of a potent induction agent followed immediately by a rapidly acting neuromuscular blocking agent to produce unconsciousness and motor paralysis provides optimal intubating conditions while minimizing the risk of pulmonary aspiration for unprepared patients.<sup>1,2</sup>

The induction agents currently used for RSI in Canada are classified as sedative-hypnotics. These include the ultra short-acting barbiturate thiopental, the benzodiazepine midazolam and miscellaneous agents such as ketamine and propofol.<sup>1</sup> Etomidate is a sedative-hypnotic chemically unrelated to other induction agents.<sup>3</sup> It provides rapid onset and recovery, minimal effects on cardiovascular parameters, and little respiratory depression or histamine release. Its protective effects on myocardial and cerebral perfusion make etomidate an ideal sedative-hypnotic for RSI in the ED. Etomidate is gaining popularity,<sup>4</sup> and a recent observational study of 610 intubations in a US university-affiliated ED found that 84% of intubations used an RSI technique and 82.5% of those cases were performed using etomidate as the induction agent.<sup>5</sup>

The purpose of this paper is to discuss the pharmacology of etomidate and review the evidence for its use as an induction agent for RSI in the ED.

## Pharmacokinetics and pharmacology

### Pharmacokinetics

Etomidate is a potent hypnotic agent without analgesic properties.<sup>6</sup> It is a carboxylated imidazole derivative with a rapid onset and short duration of action. Following an induction dose of 0.2 to 0.4 mg/kg, unconsciousness occurs within 5 to 15 seconds, which is as rapid as that attained with thiopental, propofol or ketamine.<sup>4</sup> Duration of unconsciousness after a single induction dose is approximately 5 to 15 minutes.<sup>3,4,6,7</sup>

After intravenous dosing, etomidate distribution is rapid and follows a 3-compartment pharmacokinetic model. Initial distribution half-life is  $2.6 \pm 1.3$  minutes and elimination half-life is  $4.6 \pm 2.6$  hours.<sup>8</sup> The total apparent volume of distribution is  $4.5 \pm 2.2$  L/kg, indicating extensive tissue uptake. High lipid solubility allows rapid distribution into most organs and tissues, with the highest drug concentration occurring in the brain, within 1 minute of intravenous injection. Elimination from the brain is also rapid, and the dissipation of etomidate's

hypnotic action is primarily related to redistribution to inactive tissues.<sup>8</sup>

At a physiologic pH of 7.4, etomidate is approximately 75% bound to albumin.<sup>4,8</sup> Because only the unbound fraction is pharmacologically active, changes in albumin concentration, pH or the concomitant use of other protein-bound drugs may alter the free drug fraction and clinical effects.<sup>4,8</sup> The clinical relevance of this protein binding in the setting of RSI is unknown.

Etomidate is rapidly hydrolyzed by liver and plasma esterases to an inactive metabolite, etomidate carboxylic acid.<sup>4</sup> About 75% of an injected dose is eliminated as the inactive metabolite in urine, 13% in feces and 10% in bile.<sup>8</sup> Elimination half-life is predominately determined by hepatic blood flow and perfusion; however, because the duration of hypnosis depends primarily on redistribution from the brain to inactive tissues, hepatic dysfunction does not affect the duration of clinical effects.<sup>4</sup>

### Pharmacology

Etomidate does not cause histamine release; therefore, it has minimal cardiovascular and respiratory effects, providing greater hemodynamic stability than other commonly-used agents.<sup>1,7,8</sup> Induction doses of 0.2 to 0.3 mg/kg have little effect on cardiovascular parameters like heart rate, cardiac index, stroke volume, systolic and diastolic blood pressure, pulmonary vascular resistance and systemic vascular resistance.<sup>4</sup>

Etomidate reduces cerebral blood flow and oxygen consumption, which attenuates elevated intracranial pressure (ICP) and limits ICP spikes associated with intubation.<sup>3,4,8,9</sup> Unlike thiopental and propofol, etomidate reduces ICP without decreasing arterial blood pressure or cerebral perfusion pressure.<sup>4,8</sup>

The most significant concern regarding etomidate is its effect on adrenocortical function. Etomidate inhibits the conversion of cholesterol to cortisol by a reversible and concentration-dependent block of 11- $\beta$ -hydroxylase and 17- $\alpha$ -hydroxylase.<sup>1</sup> The resulting adrenal suppression reduces cortisol and aldosterone levels approximately 30 minutes after induction for 5 to 15 hours.<sup>4</sup> Adrenal suppression is a potential problem when etomidate is used as a continuous infusion agent for days or weeks in ICU settings,<sup>3,4</sup> but there are no reports of clinically significant cortisol suppression in ED patients undergoing RSI.<sup>3,4</sup>

In a prospective, randomized clinical trial, Schenarts and colleagues assessed the adrenocortical function of 31 ED patients who received intravenous etomidate for RSI.<sup>10</sup> Patients were randomized to induction with etomidate (0.3 mg/kg) or midazolam (0.05–0.1 mg/kg), then

neuromuscular blockade was accomplished with succinylcholine (1.0–1.5 mg/kg) and adrenocortical function was assessed 4, 12 and 24 hours post induction using a cosyntropin stimulation test (CST). The CST was performed by drawing serum cortisol levels before and 1 hour after IV cosyntropin (250 mcg), and was considered normal if the pre-cosyntropin cortisol level was greater than 18 mcg/100 mL or if the post-cosyntropin cortisol level rose by more than 7 mcg/100 mL. In this trial, patients randomized to etomidate demonstrated significant differences in CSTs at 4 hours, but all patients had normal CSTs by 12 hours. And while the early abnormal CSTs suggested discernible adrenocortical dysfunction, serum cortisol levels were within normal range at all time points. The authors concluded that, following a single 0.3 mg/kg induction dose, adrenal dysfunction is minimal and resolves within 12 hours.

Other side effects include pain on injection, myoclonic movements on induction, hiccups, and vomiting after extubation.<sup>1,3,4,8</sup> Etomidate's 30% to 40% incidence of nausea and vomiting is higher than the 10% to 20% seen with thiopental.<sup>3,4</sup> However, this is usually not an issue in the ED as patients often remain intubated and sedated for hours — long enough to allow metabolism and clearance of the drug.<sup>4,8</sup> The propylene glycol diluent may cause irritation and phlebitis at the injection site, which can be minimized by administering etomidate through a large vein with a rapid intravenous infusion rate.<sup>3,8</sup>

Myoclonus is thought to result from subcortical disinhibition rather than CNS stimulation, and has not been found to be associated with seizure-like activity on the EEG.<sup>11</sup> Myoclonic activity is dose related and is observed with induction doses of 0.3 mg/kg. It is usually abolished by the co-administration of a neuromuscular blocking agent during RSI, but when etomidate is used in the absence of paralytics or other sedatives, 50% to 80% of patients experience myoclonus.<sup>1,4,8,11,12</sup>

Plewa and coworkers evaluated the safety and efficacy of etomidate in a non-RSI case series of trauma patients.<sup>13</sup> Myoclonic activity occurred in 70% of the patients — 60% mild and 10% moderate or severe. Significant orofacial myoclonus or bruxism prevented intubation in 25% of the cases, necessitating the administration of a paralytic.

Kociszewski and colleagues retrospectively evaluated 275 patients to determine intubation success rates for patients receiving etomidate ( $n = 62$ ) versus succinylcholine ( $n = 213$ ).<sup>14</sup> In this trial, physicians were permitted to use etomidate with or without succinylcholine. When intubation attempts failed after etomidate alone, rescue succinylcholine was administered. Success rates for etomidate and

succinylcholine intubations were 86.9% and 98.2%, respectively ( $p = 0.001$ ), and rescue succinylcholine was required in 11.7% of etomidate intubations. Etomidate patients were more likely than succinylcholine patients to require multiple attempts (33.3% vs. 16.3%,  $p = 0.004$ ). Myoclonus prevented intubation in one patient who received only etomidate, but myoclonus may have been a factor in other failed attempts. These reports illustrate the high incidence of myoclonus and its potential impact on intubation success when etomidate is used without a paralytic agent.<sup>13,14</sup>

## Clinical experience in the emergency department

A systematic search of MEDLINE (1966 to December 2001), EMBASE (1980 to December 2001) and PubMed (to December 2001) databases for English language, full-text reports was performed to identify articles describing the use of etomidate for RSI in the ED or similar settings. Additional published reports were identified through a manual search of reference lists in retrieved articles and in review articles. Search terms included: etomidate, rapid sequence intubation, intubation, intratracheal, respiratory tract intubation, endotracheal intubation. The search strategy was limited to human and English language trials. Case reports, case series and prospective or retrospective studies were included if they evaluated etomidate for RSI in adult or pediatric patients, and reported safety or efficacy outcomes. Articles were excluded if they evaluated a non-RSI technique or if the intubations were performed outside the emergency setting (i.e., for elective surgery). For each identified citation, both authors independently assessed article eligibility by reviewing the title and abstract. In uncertain cases or when disagreement occurred, full text articles were reviewed.

Three trials were excluded because they evaluated etomidate in elective surgical patients;<sup>15–17</sup> 1 abstract and 2 papers were excluded because they studied ED intubation without RSI;<sup>12,13,18</sup> and 1 paper comparing etomidate to succinylcholine in an aeromedical setting was excluded because it did not specifically address RSI.<sup>14</sup> One abstract<sup>19</sup> and 3 articles<sup>20–22</sup> evaluating the use of etomidate for RSI in the ED or a similar setting were identified.

## Clinical evidence

Woodard and coworkers performed a retrospective chart review to assess the hemodynamic effects of etomidate in trauma patients. Complete data were available for 56 of 66 patients who received etomidate (0.2–0.4 mg/kg) for

ED RSI.<sup>19</sup> Of these, 51 received succinylcholine (1–2 mg/kg) and 5 received vecuronium (0.1–0.3 mg/kg). The authors found that the mean systolic blood pressure change of 13 mm Hg (95% CI, 6–20 mm Hg) was not clinically significant and that no patient required intervention because of a hemodynamic problem. Of 12 patients who had hypotension before intubation, only 1 had a further decrease after intubation. Pre- and post-intubation pulse rates did not change.

In a prospective observational study, Smith and coworkers evaluated the use of etomidate in 34 patients undergoing RSI in the ED.<sup>20</sup> All patients received a defasciculating dose of vecuronium (0.01 mg/kg) followed by etomidate (0.3 mg/kg) and succinylcholine (1.5–2.0 mg/kg). Blood pressure, heart rate and oxygen saturation were measured every 2 minutes before, during and after induction, for 6 minutes. Mean changes in systolic and diastolic blood pressure were  $1 \pm 39$  mm Hg and  $0 \pm 28$  mm Hg, respectively. For patients with an initial mean arterial pressure (MAP) of 80 mm Hg or less, MAP fell by an average of 6%. No patient with an initial MAP above 80 mm Hg dropped to below 80 mm Hg. Transient myoclonus occurred in 1 patient, but did not delay intubation or cause oxygen desaturation. No patients had inadequate sedation or poor intubating conditions. The authors concluded that etomidate is a safe and effective agent for use in a range of patients undergoing RSI in the ED.

Swanson and colleagues retrospectively reviewed records from 79 patients over age 10 who underwent intubation in an aeromedical setting.<sup>21</sup> Overall, 53 (67%) received etomidate (0.2–0.4 mg/kg) and 42 of these (79%) also received succinylcholine. The intubation success rate was 96% for the 53 patients who received etomidate, but cricothyrotomies were performed in 2 patients who could not be intubated. In 46 patients with hemodynamic data, mean systolic blood pressure was  $139.11 \pm 31.21$  mm Hg before and  $137.85 \pm 32$  mm Hg after RSI. Average heart rates were  $101.59 \pm 23.95$  beats/min before and  $97.76 \pm 23.45$  beats/min after RSI ( $p = ns$ ). The authors concluded that etomidate is safe and effective for RSI in the aeromedical setting.

Sokolove and collaborators retrospectively evaluated the use of etomidate in 100 pediatric patients (10 years or younger) undergoing RSI, looking for evidence of clinically important hypotension or adrenal insufficiency.<sup>22</sup> Clinically important hypotension was defined as a decrease in systolic blood pressure to less than 1 SD of the mean for age, while clinically important adrenal insufficiency was defined as the need for exogenous corticosteroid replacement for suspected adrenal insufficiency at any time during

hospitalization. In this study, the mean etomidate dose was  $0.37 \pm 0.15$  mg/kg (range 0.05–0.9 mg/kg). Paralytics were given in 99% of cases (54% succinylcholine, 39% rocuronium, 6% vecuronium) and atropine in 37% of cases. Hemodynamic data were available for 84% of the intubations. The mean systolic blood pressure was  $121 \pm 25$  mm Hg prior to intubation and  $120 \pm 27$  mm Hg post-intubation, and clinically important hypotension occurred in 4 patients (4.8%). Fourteen patients received corticosteroids during hospitalization, but none were for suspected adrenal insufficiency. The authors concluded that there is a low incidence of clinically important hypotension and no evidence of clinically important adrenocortical suppression when etomidate is used for ED RSI in pediatric patients.

## Limitations

The prospective study by Smith and coworkers is limited by its small sample size.<sup>20</sup> The study was observational, and results were analyzed descriptively. Measurements of blood pressure, MAP and heart rate were evaluated for only the first 6 minutes, and a longer monitoring period might have revealed delayed adverse effects. Etomidate was not compared with other induction agents in a blinded or controlled manner. This study does not allow definitive conclusions about the role of etomidate relative to other available agents, but it does demonstrate utility and safety (for RSI) in a small number of patients.

The studies conducted by Swanson and colleagues<sup>21</sup> and Sokolove and coworkers<sup>22</sup> had methodological flaws inherent in their retrospective design. These authors depended on the accuracy and completeness of medical records and excluded patients with incomplete chart data (hemodynamic data was available for 87% and 84% of their patients, respectively). Neither study controlled for concurrently administered medications such as benzodiazepines, opioid analgesics and atropine, which could have affected hemodynamic parameters.

Sokolove and coworkers evaluated children 10 years and under.<sup>22</sup> The product monograph for etomidate does not recommend etomidate for induction of anesthesia in patients under 10 years because of the lack of data to make dosage recommendations.<sup>23</sup> The dose range of 0.05 to 0.9 mg/kg used in the study was wide and not discussed in detail. Definitive conclusions about pediatric dosing cannot be made from this study. The authors used “need for corticosteroid therapy” during hospitalization as an indicator of clinically significant adrenal insufficiency, but this is an unreliable and indirect measure of adrenal function.

## Emergency medicine perspectives

The pharmacological and safety profiles of etomidate offer many advantages for RSI in the ED. Its onset of action is rapid and predictable, and its duration of action is comparable to commonly used induction agents such as thiopental, ketamine and propofol. Etomidate does not cause histamine release and, unlike most currently used agents, it has minimal effects on cardiovascular parameters. It can therefore be used safely in hemodynamically unstable patients and those with myocardial ischemia or infarction.<sup>4</sup> Etomidate is cerebroprotective, with the ability to decrease ICP and maintain cerebral perfusion pressure, making it an ideal agent for the patient with head injuries. Etomidate has minimal respiratory effects relative to thiopental or propofol; however, in patients with asthma or reactive airway disease, ketamine remains the induction agent of choice because of its bronchodilating effects.<sup>3,4</sup> Of the currently available induction agents, etomidate offers the most favourable safety profile and is the least likely to produce adverse effects in patients with unknown or untreated medical conditions.<sup>4</sup>

An intravenous induction dose of etomidate (0.3 mg/kg) coupled with a neuromuscular blocking agent will rapidly produce favourable intubating conditions with a return of consciousness in 5 to 15 minutes. For patients with tachycardia and hypertension, fentanyl premedication can be co-administered to enhance cardiovascular stability.<sup>9</sup>

## Conclusion

Etomidate has major pharmacologic advantages as an induction agent for RSI in the ED. It is well studied in the ED and should be adopted for specific patient groups. It is not currently available on the Canadian market, but is available through the Special Access Program at Health Canada ([www.hc-sc.gc.ca/hpb-dgps/therapeut/htmleng/edrp.html](http://www.hc-sc.gc.ca/hpb-dgps/therapeut/htmleng/edrp.html)). Some Canadian institutions have obtained etomidate through this program and are gaining experience with this valuable agent.<sup>24</sup>

**Competing interests:** None declared.

**Acknowledgements:** We thank Drs. Riyad Abu-Laban and David Harrison, Department of Emergency Medicine, Vancouver Hospital and Health Sciences Centre, Vancouver, BC, for their editorial contribution during the preparation of this manuscript.

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