

## August 2006 Journal CME

### New Protocols, New Questions – Part 1: Etomidate

On or around January 1<sup>st</sup> and July 1<sup>st</sup> of each year, New York City REMAC institutes within its EMS protocols those changes that have been approved by the Committee within the preceding six months. In some instances, those changes could be considered rather small, such as when the order of treatment steps within a protocol is rearranged, while others may be much more dramatic.

Certainly the changes that have taken place in the New York City EMS protocols over the past eight months could not be considered minor. We have added etomidate to our airway management protocols and approved the use of continuous positive airway pressure (CPAP) in the prehospital system. And, as you will see in this month's bulletin, we have further overhauled the Region's protocols in recent months.

The resuscitation protocols have undergone a myriad of changes in order to incorporate the latest science and the recommendations found in the 2005 Guidelines put forth by the American Heart Association (AHA), International Liaison Committee on Resuscitation (ILCOR), and the European Resuscitation Council (ERC). Ipecac has been eliminated from the overdose protocol. Narcan has been approved for use via the intranasal route when an appropriate "atomizer" is available. And the head injury protocol has been modified to include both recommendations for airway management and the treatment of on-going seizures following a head injury.

With these changes undoubtedly come questions among you, the field providers on whom we rely to provide the emergency medical care set forth in these protocols. These questions will relate to the rationale behind REMAC's decisions, the new technologies and drugs introduced within these pages, and the reasons that prior protocols were changed.

In order to begin to address some of those questions, the Office of Medical Affairs will be offering a series of CME articles related to the protocol changes of the 2006 calendar year. This, the first in the series, will discuss the drug etomidate. Future articles will then focus on vasopressin, amiodarone, calcium chloride, and the use of CPAP, as well as carbon monoxide monitoring.

#### Etomidate – The ideal drug for facilitated intubation?

The perfect drug to allow for the endotracheal intubation of a patient will vary depending upon the person performing the procedure and the clinical setting in which it is performed. In the prehospital setting, particularly for those EMS agencies whose use of paralytic agents is neither possible nor medically appropriate, etomidate may approach just such an ideal.

Etomidate was first developed in the 1960s and brought into use in the clinical environment in the following decade. Initially there was a great deal of concern about the drug because of its effects on the adrenal gland function (described below). But over the past forty years, our understanding of the pharmacokinetic and pharmacodynamic properties of this agent have brought it into favor in the emergency medicine community where many people consider it the drug of choice for facilitated intubation.

### **Pharmacology / Chemistry**

Etomidate is an imidazole derivative agent with the chemical structure shown in Figure 1. Like many drugs, it exists in two forms (essentially, a leftward and rightward oriented chemical structure), but only one isomer provides the physiologic effects for which it is used. Because of its relative water insolubility, it is suspended in a 35% propylene glycol solution that has an osmolality of 4,640 mOsm/L.

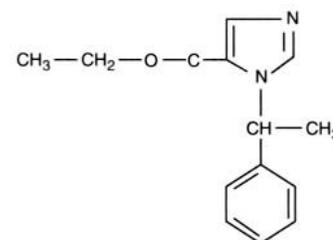
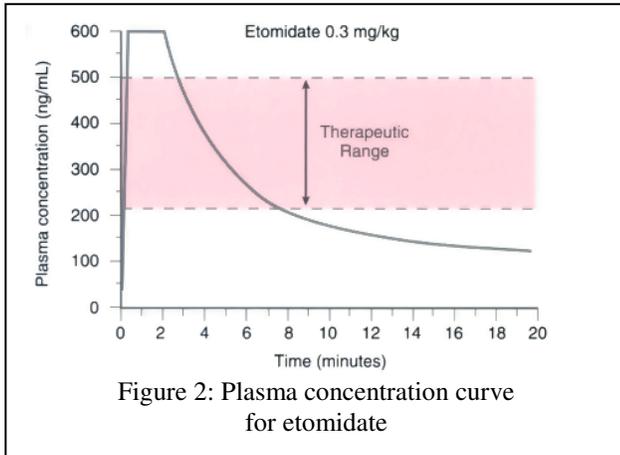


Figure 1: Etomidate's chemical structure

*(Now if I were reading that last paragraph, my first reaction would be to rub my eyes and pull up a pillow, expecting the rest of the article to be really technical and sleep inducing. Why even mention its osmolality?)*

*Consider for a moment that the osmolality of D50 is 2,530 mOsm/L. Now think back to the degree of warning that you received about D50 extravasation and how you should be sure to administer it in a slow enough fashion to ensure that the intravenous line doesn't "blow." Since the osmolality of etomidate is nearly twice that of D50, you can imagine the pain, tissue injury, and swelling that would occur if this were given via any parenteral means other than the intravenous route, or if it extravasated into the tissue surrounding a "lost" intravenous site. Now that we hopefully have your attention, let's continue...)*

Etomidate has interesting pharmacokinetics and pharmacodynamics as well. After a single intravenous dose, the levels within the brain peak within one minute, suggesting that one can expect a fairly rapid onset following intravenous administration. Curiously, unlike other anesthetic or induction drugs, this rapid onset is not overly sensitive to blood pressure. In fact, one animal model showed that the initial distribution of the drug was unaffected by mean arterial pressures as low as 50 mmHg. This combined with the blood pressure response to the drug (described below) allow its use in a wide variety of clinical settings, including various shock states.



Once administered, the drug is slowly metabolized by the liver. Between 2.9 and 5.3 hours after administration, approximately 50% of the drug will have been metabolized. In patients with liver disease or impaired hepatic circulation, this time may be even longer. And yet the clinical effects of the drug last only minutes (Figure 2). Another study estimated that each 0.1mg/kg administered provides 100 seconds of loss of consciousness.

This short duration of action is due to a rapid redistribution of the drug among the body's tissues. Etomidate's eventual volume of distribution is 2.5-4.5 L/Kg. This is because the drug is highly protein bound (over 75%).

### **Clinical Effects**

Etomidate exerts its effects by inducing a hypnosis state, and it should be noted that it has no analgesic properties. Although its mechanism is not entirely clear, the drug appears to act by stimulating GABA receptors within the central nervous system and by depressing the function of the reticular activating system within the brainstem. As mentioned above, the effect typically lasts from 5-8 minutes following the administration of a 0.3mg/kg dose, making its duration (and therefore the potential time during which it may result in an unmanageable airway) much shorter than either diazepam or midazolam, the other options under the REMAC protocols. Yet, this short duration also suggests that the patient will likely need additional sedation in order to maintain the airway once the etomidate effects have worn off.

Within the central nervous system (CNS), it has been demonstrated that a single dose of etomidate results in a reduction in cerebral oxygen consumption of up to 45%. By depressing CNS activity, the drug results in less cerebral oxygen consumption, a benefit for patients whose hypoxia or hypoperfusion has diminished the patient's oxygen delivery capacity.

Etomidate also results in a reduction in cerebral blood flow, though not to as great a degree as cerebral oxygen consumption is reduced. Because cerebral blood flow is reduced by 34% in the setting of a 45% reduction in cerebral oxygen demand, the net result is an increased delivery-to-demand ratio for oxygen within the brain, also a potential benefit for patients whose hypoxia or hypoperfusion has resulted in cerebral hypoxia.

The final beneficial effect within the central nervous system is related to its effects on intracranial pressure (ICP). When given in a 0.3mg/kg dose, etomidate causes a 50% reduction in ICP in adult patients with increased intracranial pressure and a statistically significant reduction among pediatric patients as well. This effect not only extends for the duration of the unconscious period, but some residual effect is maintained even after intubation is accomplished. Because the drug does not affect the reactivity of the vasculature, further ICP reduction may be accomplished through appropriate hyperventilation, especially if performed in the setting of arterial or end-tidal carbon dioxide monitoring.

One potential adverse effect of etomidate on the CNS is the potential for increased activity within ectopic foci. This may result in the stimulation of seizure activity. This same effect on electrical activity within the brain may also result in myoclonic activity, possibly making the patient more difficult to intubate. It is important for providers to distinguish between these two phenomena, as only the true seizures require treatment with benzodiazepines.

Within the respiratory tract, etomidate does not cause histamine release in either healthy patients or those with reactive airway disease. As such, it is not likely to induce either increased respiratory secretions or bronchospasm. Its effects on ventilation are also minimal, typically demonstrating a brief period of hyperventilation followed by a similarly brief period of apnea. Although this may result in a slight (~15%) increase in carbon dioxide levels, it does not appear to affect the patient’s oxygenation during this period.

Etomidate also demonstrates advantages over other drugs approved by REMAC for facilitated intubation. Table 1 demonstrates the effects of etomidate, diazepam, and midazolam on cardiovascular parameters. As you can see, etomidate is relatively similar to diazepam, and both drugs have much less potential than midazolam to depress cardiovascular function. Similar effects with respect to mean blood pressure have been reported in pediatric patients.

	<b>Diazepam</b>	<b>Midazolam</b>	<b>Etomidate</b>
<b>Heart Rate</b>	<b>- 9 to - 13%</b>	<b>- 14 to + 12%</b>	<b>- 5 to + 10%</b>
<b>Mean Blood Pressure</b>	<b>0 to + 19%</b>	<b>- 12 to + 26%</b>	<b>0 to + 17%</b>
<b>Systemic Vascular Resistance</b>	<b>-22 to + 13%</b>	<b>0 to + 20%</b>	<b>- 10 to + 14%</b>
<b>Stroke Volume</b>	<b>0 to + 8%</b>	<b>- 28 to - 42%</b>	<b>0 to +20%</b>

Table 1: Cardiovascular effects of REMAC-approved drugs for facilitated intubation

The endocrine effects of this drug are the primary reason that its use has been so slowly accepted within the medical community during its forty-plus years of existence. An article in 1983 demonstrated an increase in deaths among patients receiving continuous infusions of etomidate for sedation purposes. This effect was attributed to the depressed activity of the adrenal glands that etomidate produces, a finding confirmed in another ICU study in which patients were given supplement doses of corticosteroids. Although this same action on adrenal function has been shown after even single doses of

etomidate, there has never been any evidence in the literature that these short-term effects have any impact on patient outcome, and they are therefore considered clinically insignificant by many.

Other adverse effects that may come about from the use of etomidate include pain at the site of injection, vomiting, and hiccups. Pain at the site can be minimized by administering the drug via a slow intravenous push. Nausea and vomiting have been reported in nearly one third of patients receiving the drug, though this is more common in patients receiving the drug for procedural sedation or anesthesia as opposed to those undergoing facilitated intubation. Like myoclonus, the hiccups are believed to be centrally mediated and due to the drug's effects on CNS electrical activity. While some studies report these effects in as many as 70% of patients, more recent reviews including those in the prehospital and aeromedical setting report a very low incidence of such side effects.

### **Reported Success**

Only three studies have really addressed the success of etomidate use in the prehospital setting. Two of those studies were performed in the aeromedical setting, and one was performed in a ground-based ALS service.

In 2003, Bozeman and Young reported a two-year experience with etomidate. In their aeromedical system, forty-four patients received only etomidate for the purpose of facilitated intubation. 89% of these patients were able to be intubated, though 16% were considered difficult intubations and required three or more attempts. Of those forty-four patients, eight did vomit during their unconscious period, three patients (7%) developed trismus that prevented intubation, and one child experienced a seizure. It should be noted that this study was both small and utilized a larger dose of etomidate (0.5mg/kg) than will be allowed under our REMAC protocols.

In a follow-up study in 2006, Bozeman and colleagues compared the use of etomidate alone to the use of etomidate plus a neuromuscular blockade agent, namely succinylcholine. They found that 63% of the patients who initially received only 0.3mg/kg of etomidate were unable to be intubated and required either additional sedation or neuromuscular blockade. They also reported that the paramedics and nurses reported visualization of the glottic opening in only 12% of patients.

Also in 2006, the first peer-reviewed article addressing the use of etomidate in the ground prehospital system was published. In that article Jacoby and colleagues reported on a trial where they randomly decided to give patients in need of facilitated intubation either intravenous midazolam or etomidate. They found no difference in the ability of the paramedics to intubate (75% for midazolam versus 76% for etomidate), the perceived difficulty of the intubation, or the need for additional sedation.

These studies certainly don't suggest that etomidate is the greatest drug since oxygen. But they do point out a couple of very important points: 1) Airway visualization is likely to be difficult even with

etomidate use, demonstrating the importance of using a secondary confirmation device following the intubation attempt. 2) Not every patient receiving etomidate will be able to be intubated, reinforcing the need for strong basic airway management skills. 3) The frequency of side effects is relatively low, though the complications mentioned above do occur and must be anticipated in order to allow for a rapid response to their occurrence.

## **Conclusions**

The addition of etomidate to the New York City REMAC protocols and its recent expansion into a larger number of protocols provides an additional tool in the management of patients' airways. Because of the hemodynamic properties of the drug, its use in even hemodynamically unstable patients expands its target population beyond those for whom other drugs might be used. Its effects on cerebral metabolism, cerebral blood flow, and ICP make it an ideal agent for the management of head injury patients, patients with a cerebrovascular accident or hemorrhage, and all other patients whose brain may be either hypoxic or hypoperfused. Its effects on the ability of the paramedics in the Region to provide advanced airway management will be something that we will have to continue to monitor.

Finally, when using etomidate, keep the following points in mind:

- the dosing listed in protocol is 0.3mg/kg, not to exceed 20mg
- clinical effects are short-lived (5-8 minutes), so be prepared to intubate before administering the drug
- in patients who are conscious or semi-conscious, slower IV administration may minimize the pain that the patient experiences at the injection site
- although patients with intracranial injuries may benefit from etomidate prior to their intubation, lidocaine should still be administered
- the high likelihood of vomiting (7-30%) necessitates the presence of a working suction unit during intubation attempts
- the patient will be neither apneic or paralyzed following etomidate administration, and this may lead to a difficult time visualizing or managing the airway
- seizures that occur after etomidate administration should be treated with benzodiazepines, but myoclonic activity should not
- additional sedation (benzodiazepines) may be needed after intubation, so ask medical control for both at the time of the initial call

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## **AUGUST 2006 JOURNAL CME QUIZ – “New Protocols - Etomidate”**

**\*\* DO NOT RETURN THIS PAGE – SEND ANSWER SHEET ONLY (page 12) BY AUG. 31\*\***

1. Etomidate belongs to which group of medications?
  - a. Benzodiazepine
  - b. Hypnotic
  - c. Barbiturate
  - d. Paralytic
  - e. Analgesic
2. The administration of etomidate results in which of the following effects on intracranial pressure?
  - a. Decrease
  - b. Increase
  - c. No change
3. As compared to D50, etomidate is:
  - a. Isotonic
  - b. Hypertonic
  - c. Hypotonic
4. The chemical half-life of etomidate in the human body following intravenous administration of 0.3mg/kg is:
  - a. Between 2.9 and 5.3 hours
  - b. Eight to ten minutes
  - c. Less than one minute
  - d. Dependent on blood pressure
  - e. None of the above
5. Which of the following is not a common side effect of etomidate?
  - a. Myoclonus
  - b. Seizures
  - c. Vomiting
  - d. Laryngospasm
  - e. Pain at the injection site
6. True or false: The time from intravenous administration of etomidate until the onset of the unconscious state is not affected by mild to moderate hypotension.
  - a. False
  - b. True
7. The clinical effects of etomidate following the administration of 0.3mg/kg is:
  - a. Eight to ten minutes
  - b. Less than one minute
  - c. Dependent on blood pressure
  - d. Between 2.9 and 5.3 hours
  - e. None of the above
8. Which of the following statements regarding the literature related to the prehospital use of etomidate is correct?
  - a. There have been three studies related to EMS use of etomidate, but all were performed in the aeromedical setting.
  - b. The use of etomidate has been shown to result in a dramatic increase in intubation success when compared with midazolam.
  - c. In one study, nearly nine out of ten patients were able to be intubated after etomidate administration.
  - d. Etomidate use leads to only 12% of patients' glottic openings that were not able to be visualized by paramedics.
  - e. All of the above are incorrect.
9. Advantages of etomidate over midazolam include all of the following except:
  - a. Less potential for induced seizures.
  - b. Less potential for secondary hypotension or blood pressure reduction.
  - c. Less reduction in myocardial stroke volume.
  - d. Shorter duration of action.
  - e. All of the above are correct.

10. The REMAC-approved weight-based dosing for etomidate in the New York City protocols is:
- a. 0.5 mg/kg
  - b. 0.1 mg/kg
  - c. 0.2 mg/kg
  - d. 0.3 mg/kg
  - e. 0.4 mg/kg