Etomidate: Single dose
Adrenal Suppression

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Introduction

- **Etomidate: To suppress or not to suppress?**
  - Recent literature and clinical experience point to etomidate as a major cause of adrenal suppression in ICU and trauma patients from as little as a single induction dose.
  - We will review the pharmacology of etomidate and discuss the recent literature regarding its role in adrenal suppression.
Etomidate: History/Characteristics

- Etomidate was introduced into clinical practice in 1972. It rapidly gained popularity for induction and maintenance of anesthesia secondary to its rapid onset/offset time and wider safety margin. The use of etomidate dramatically decreased in 1983 after it was discovered that etomidate inhibited steroid synthesis.¹

- Imidazole derivative

- 2 isomers, only the (+) isomer is hypnotic

- Insoluble in water therefore standard solution in US is 2mg/ml dissolved in propylene glycol
Etomidate: Mechanism of Action (recently Discovered)

- It has long been hypothesized that Etomidate’s anesthetic effect was mediated by GABA receptor modulation which has been recently confirmed.\(^2,3,4\)
- Binds to The GABA\(_A\) receptor.\(^2\)
Etomidate: Metabolism/Induction/Maintenance

- Metabolized in liver primarily by ester hydrolysis and secondarily by N-dealkylation
- Excreted by the kidney (85%) and bile (13%)
- Induction dose is 0.2-0.6 mg/kg
- Each 0.1 mg/kg provides ~100 seconds of loss of consciousness
- Maintenance dose ~10 mcg/kg/min (plasma concentration of 300-500 ng/ml)

Reference # 1 (Miller Anesthesia)
Etomidate: Pharmacokinetics

- Open 3 compartment model
  - 1. Initial distribution half life 2.7 minutes
  - 2. Redistribution half life 29 minutes
  - 3. Elimination half life of 2.9-5.7 hrs

- Hypnotic effect dissipated via redistribution – no prolongation in liver failure.

Reference #1 (Miller Anesthesia)
Etomidate: Adverse Reactions

- Pain on injection
- n/v
- Myoclonus
- Hiccups
- Adrenal Suppression
- Thrombophlebitis

Reference # 1 (Miller Anesthesia)
Etomidate: Endocrine effect

- Blocks 2 enzymes in the cortisol pathway in a dose dependent reversible fashion
  - 1. 11β-hydroxylase
  - 2. 17α-hydroxylase
1985 Duthie and associates showed induction dose etomidate decreased cortisol levels up to 1 hr post-op.\textsuperscript{15}

Zed et al discussed the use of etomidate for RSI in the ED. The review states the transient adrenal insufficiency may be detrimental in patient’s requiring intubation in the ED, especially those in septic shock.\textsuperscript{5}

Lundy et al present a case report suggesting the single induction dose (0.3 mg/kg) of etomidate as the cause of acute and clinically significant adrenal insufficiency in their patient.\textsuperscript{6}

In a review Jackson concluded that single dose etomidate increases morbidity and mortality in patients with septic shock.\textsuperscript{7}

According to Bloomfield & Noble 1 in 5 critically ill patients who receive etomidate will die if not concurrently administered corticosteroids.\textsuperscript{10}
Adrenal Insufficiency in the Literature

- Mohammad et al showed in a retrospective study of 152 septic patients an increased incidence of adrenal insufficiency in patients who received etomidate when compared to those who did not receive etomidate.\(^8\)

- An editorial by Annane in 2005 called for ICU physicians to abandon the use of etomidate.\(^9\) This followed his article in 2002 where a subgroup of septic shock patients who received etomidate had a higher incidence of adrenal insufficiency.\(^{17}\)

- A prospective cohort study by Malerba et al indicated a single dose of etomidate caused a 12 fold increase in incidence of adrenal insufficiency for up to 24 hours.\(^{16}\)
“Acknowledging the good while accepting the bad,” Murray and colleagues state that some patients may be too unstable for any other induction medication. ¹¹

Bloomfield and Noble call for re-evaluation of the safety of Etomidate. ¹²(That have a justifiable reason for using etomidate and document it- medico-legal)

Annane states ICU physicians should abandon use but understands the need for the drug in hemodynamically unstable patients; therefore in this instance the patients should be aggressively supplemented with steroids. ⁹,¹⁷
“Efficient Short-Term Control of Hypercortisolaemia by Low-Dose Etomidate in Severe Paediatric Cushing’s Disease.” ¹³

“Etomidate Use for Cushing’s Syndrome Caused by an Ectopic ACTH Producing Tumor.” ¹⁴
A randomized controlled trial needs to be done to determine the degree of adrenal suppression from single dose etomidate.

Continue to use etomidate secondary to its hemodynamic stability but monitor cortisol level post administration or pre-treat with steroid.
References


8. Mohammad et al., The incidence of relative adrenal insufficiency in patients with septic shock after the administration of etomidate, Critical Care 2006, 10:R105. online at http://ccforum.com/content/10/4/R105


13. Greening et al., Efficient Short-Term Control of Hypercortisolaemia by Low-Dose Etomidate in Severe Paediatric Cushing’s Disease, Hormone Research 2005; 64:pp 140-143.


Questions?