

## Pharmacology of Rapidly Metabolized Etomidate Derivatives

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Harvard Medical School  
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## Disclosures

- The Massachusetts General Hospital has filed patent applications related to the technology that I will present.
- My colleagues and I, our laboratories, the DACCPM, and the MGH could receive compensation from their development, licensing, or sales.
- I have equity in and consult for a start-up company that has licensed this technology for development.

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"Under disclosure rules, I'm required to tell you I own stock in the company whose drug I'm prescribing."

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# Outline

- 🌐 Etomidate
- 🌐 MOC-etomidate: The prototype “soft” analog
- 🌐 2<sup>nd</sup> Generation MOC-etomidate analogs

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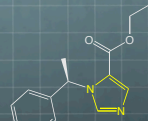
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# Etomidate

- 🌐 Imidazole-based drug developed in 1960's by Janssen Pharmaceuticals
  - 🌐 For use as an anti-fungal agent
  - 🌐 Imidazole-based antifungals bind to the cytochrome P450 enzyme 14- $\alpha$ -demethylase
  - 🌐 Inhibit synthesis of the steroid ergosterol, a critical component of the fungal cell membranes
  - 🌐 Caused hypnosis when tested in rats
  - 🌐 High therapeutic index (Lethal dose/ Hypnotic Dose)
 

🌐 Etomidate TI:	26
🌐 Barbiturates and Propofol TI	4




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# Introduction of Etomidate into Clinical Practice

- 🌐 Introduced into clinical practice in 1972
- 🌐 Usage
  - 🌐 Induction and maintenance in the OR
  - 🌐 Sedation in the ICU

*Anaesthesia*, 1982, Volume 37, pages 765-771

**Safer sedation for ventilated patients. A new application for etomidate**

D.L. Edbrooke, MRCS, LRCP, FFARCS and D.M. Newby, MB, ChB, FFARCS, Consultant Anaesthetist, S.J. Mather, MB, BS, DRCOG, FFARCS, Senior Registrar in Anaesthetics, A.M. Dixon, MB, ChB, Registrar in Anaesthetics, B.S. Hebron, BPharm, MPS, PhD, Research Pharmacist, Intensive Care Unit, Kerthelium District General Hospital, Oakwood, Rotherham S69 7UD

🌐 *“This technique may be recommended as an alternative to conventional methods of sedation for ventilated patients”.*

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## Ledingham and Watt Letter

1270

THE LANCET, JUNE 4, 1983

### Letters to the Editor

#### INFLUENCE OF SEDATION ON MORTALITY IN CRITICALLY ILL MULTIPLE TRAUMA PATIENTS

SIR,—At the recent 2nd European Meeting on Intensive Care<sup>1</sup> we reported an increased case fatality rate amongst patients with multiple injuries who had been admitted to an intensive therapy unit. This is a preliminary account referring only to the main elements of a more detailed investigation. In a group of 428 patients the death rate fluctuated between 22% and 29% during the period

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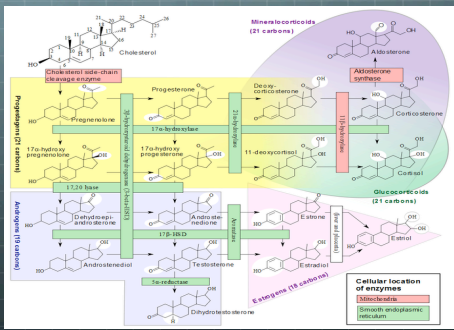
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## Etomidate Inhibits 11 $\beta$ -Hydroxylase




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## Why Does Adrenocortical Suppression Last So Long?

- Etomidate Potency
  - Anesthesia: 1  $\mu$ M
  - Adrenocortical suppression: 10 nM
- Etomidate is 100X more potent an inhibitor of adrenocortical function than it is an anesthetic
- When we give a standard etomidate induction dose, we are giving a massive overdose with respect to adrenocortical suppression
- Etomidate elimination half-life: 3-5 hours

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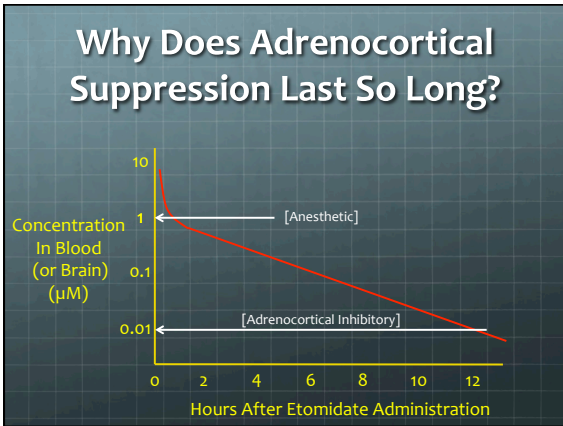
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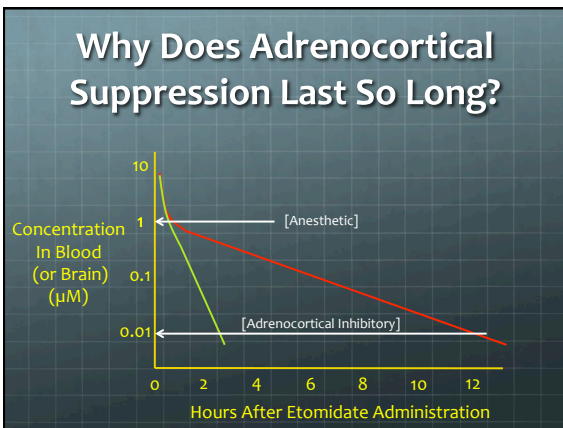
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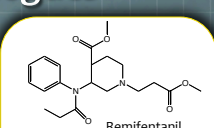
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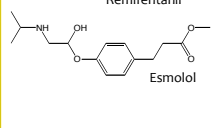
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### “Soft” Analogues

- Add an esterase-susceptible moiety
  - Remifentanyl
  - Esmolol
- Metabolic half-lives ~ 10 min
- Metabolized by tissue and/or blood esterases
- Metabolites are carboxylic acids that have reduced potencies (~100-4000X less)



Remifentanyl



Esmolol

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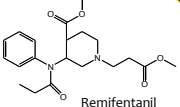
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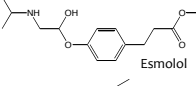
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### “Soft” Analogues

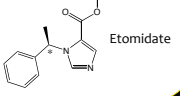
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Remifentanyl



Esmolol



Etomidate

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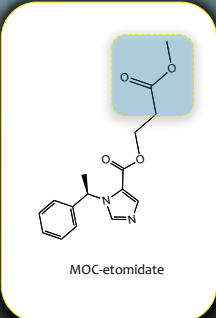
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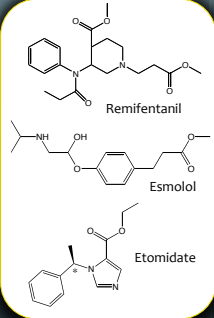
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### MOC-etomidate



MOC-etomidate



Remifentanyl  
Esmolol  
Etomidate

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### MOC-etomidate

- Hypnotic activity (albeit ~5x less potent than etomidate)
- Enhances GABA<sub>A</sub> receptor function
- Hemodynamically stable
- High therapeutic index
- Extremely rapidly metabolized by esterases (20 sec)
- Doesn't cause prolonged adrenal suppression
- Ultra-short duration of anesthesia

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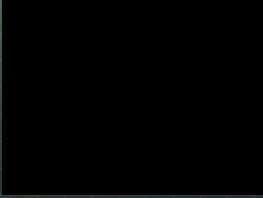
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## Equi-Anesthetic Doses

MOC-etomidate (20 mg/kg)



Etomidate (5 mg/kg)



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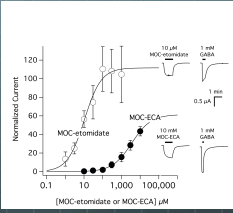
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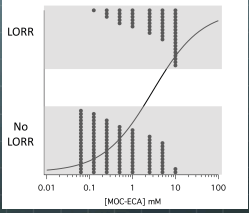
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## MOC-etomidate Metabolite





Assay	Etomidate	MOC-etomidate	MOC-ECA	MOC-etomidate/MOC-ECA
Loss of righting reflexes in tadpoles (EC <sub>50</sub> )	2.3 ± 0.13 μM*	8 ± 2 μM*	2800 ± 640 μM	1/350
Direct activation of GABA <sub>A</sub> receptors (EC <sub>50</sub> )	10 ± 2.5 μM	3500 ± 630 μM	30 ± 7 μM	1/350
Inhibition of in vitro cortical synthesis (IC <sub>50</sub> )	0.0013 ± 0.0002 μM*	0.10 ± 0.02 μM	30 ± 7 μM	1/200

EC<sub>50</sub> = 50% effective concentration; GABA<sub>A</sub> = γ-aminobutyric acid type A; IC<sub>50</sub> = half-maximal inhibitory concentration.

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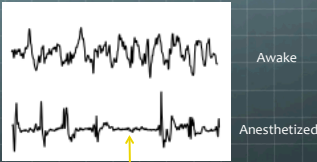
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## Anesthetic-Induced Changes in EEG Burst Suppression



**Burst Suppression**

Burst Suppression Ratio (BSR) = Fraction of time EEG is suppressed

The higher the BSR, the deeper the anesthesia

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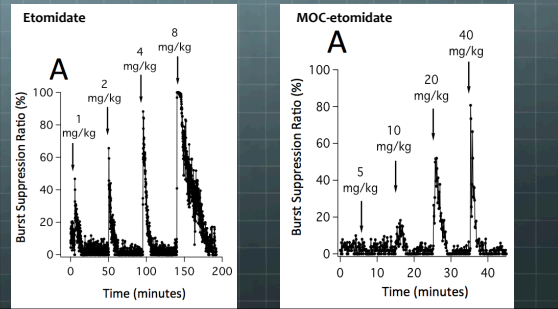
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## Anesthetic-Induced Changes in EEG Burst Suppression



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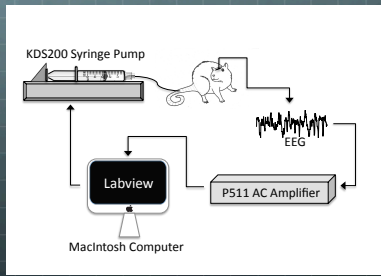
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## Closed-Loop Computer-Controlled MOC-etomidate Infusions



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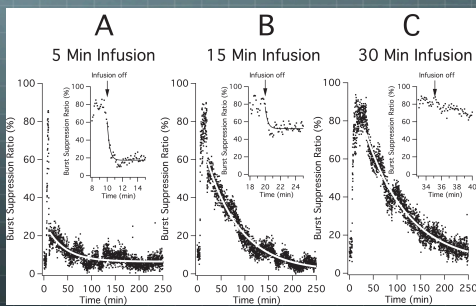
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## MOC-etomidate Infusions



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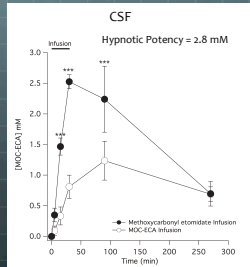
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## MOC-etomidate Infusions




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## Conclusion

- MOC-etomidate's metabolite was building up in the brain
- Slow EEG recovery
- Slow awakening from anesthesia
- Potentially slow adrenocortical recovery
- Solution: Slow MOC-etomidate metabolism down

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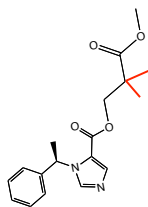
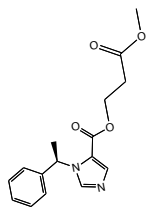
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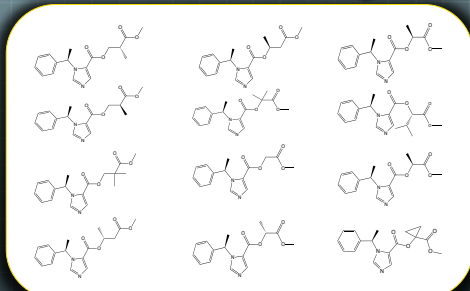
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## 2<sup>nd</sup> Generation Soft Etomidate Analogues




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## 2<sup>nd</sup> Generation Soft Etomidate Analogues

- 🌐 Metabolic half-lives (in rat blood) varied by >100-fold from <2 sec to 10 min.
- 🌐 Anesthetic potencies in rats ranged ~ 10-fold.

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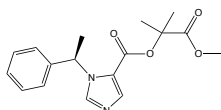
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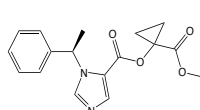
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## DMMM & CPMM

DMMM



CPMM




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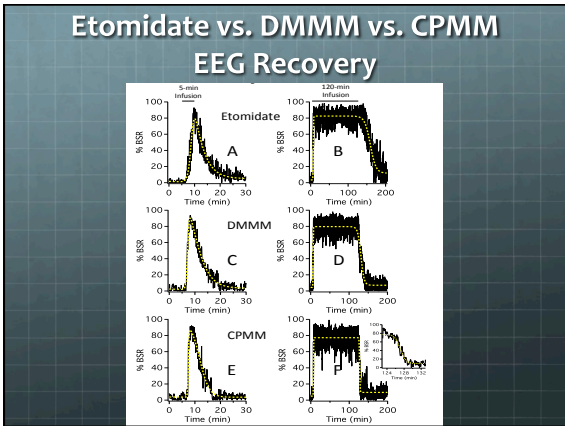
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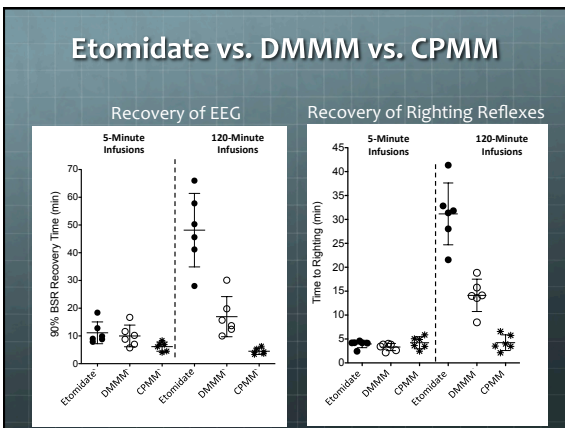
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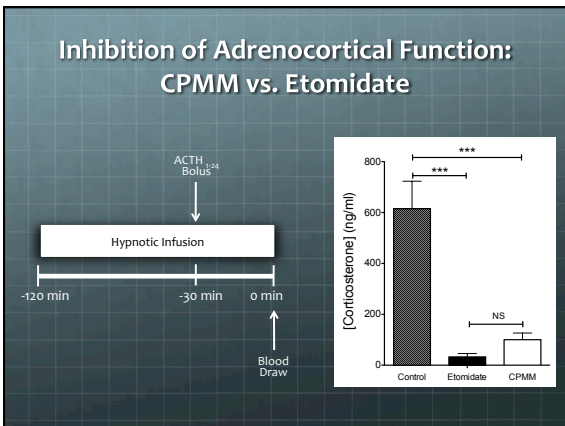
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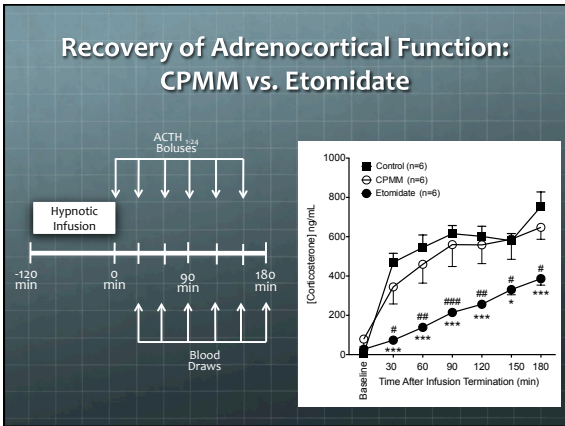
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- ## Conclusions
- Soft analogue strategy can be applied to etomidate
    - Accelerate anesthetic recovery
    - Accelerate adrenal recovery
  - MOC-etomidate is relatively low potency and very rapidly metabolized
    - Metabolite buildup
    - Delayed recovery
  - CPMM
    - More potent and slowly metabolized than MOC-etomidate
    - Much lower dosing (~50-fold) than MOC-etomidate
    - Significantly less metabolite buildup than MOC-etomidate
    - Rapid and context-insensitive anesthetic recovery
    - Rapid adrenal recovery
    - Clinical trials expected to begin by the end of 2013

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## Thank You

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