Principles of Pharmacodynamics & Pharmacokinetics

Pharmacokinetic & Pharmacodynamic approaches to Designer Drugs

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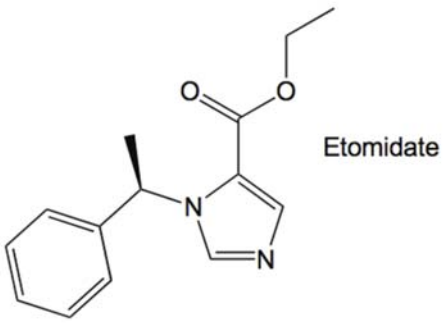
Etomidate (Janssen 1972)



Etomidate

EC_{50} = 2 μM

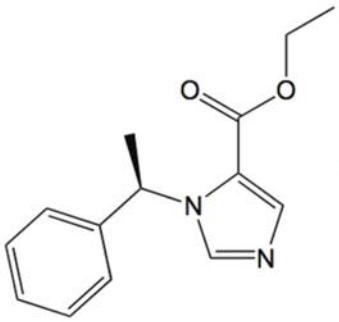
Intravenous anaesthetic
rapidly acting
induction of anaesthesia (bolus)
and sedation (ITU)

-hemodynamic stability (used in critically ill patients)

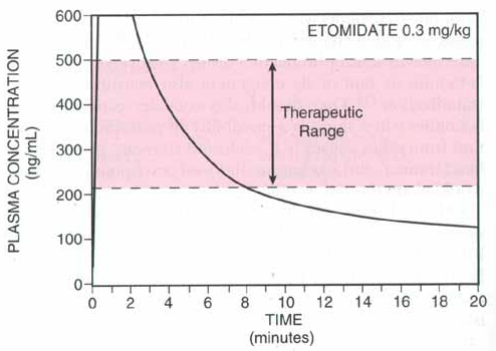
-amnestic
-not analgesic

Potentitates $GABA_A$ receptors

Etomidate (Janssen 1972)



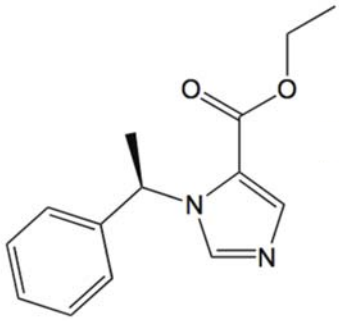
Pharmacokinetics – 3 compartment model



EC_{50} = 2 μM

$t_{1/2}$ (distribution) = 3 minutes
$t_{1/2}$ (redistribution) = 30 minutes
$t_{1/2}$ (elimination) = 4 hrs

Etomidate (Janssen 1972)



IC_{50} ~ 20 nM

11β-hydoxylase inhibition

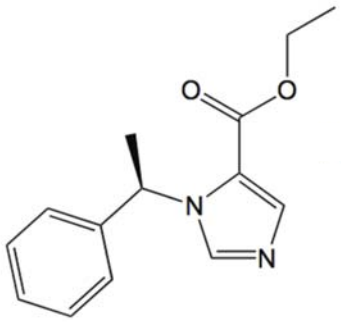
<u>Side effects</u>

Suppresses corticosteroid synthesis by inhibition of 11β-hydoxylase enzyme (cytochrome P450 family)

Increased adrenal corticosteroid production – normal stress response in critically ill patients

Etomidate associated with increased mortality in critical patients in ITU – no longer used for long term sedation

Etomidate



IC_{50} ~ 20 nM

11β-hydoxylase inhibition

Half time for elimination slow (4 hrs)

Very potent inhibitor of 11β-hydoxylase at much lower than anaesthetic dose

Even after a single bolus (induction) 11β-hydoxylase inhibition can occur up to 24hrs later

May not be good for critically ill patients even as induction agent

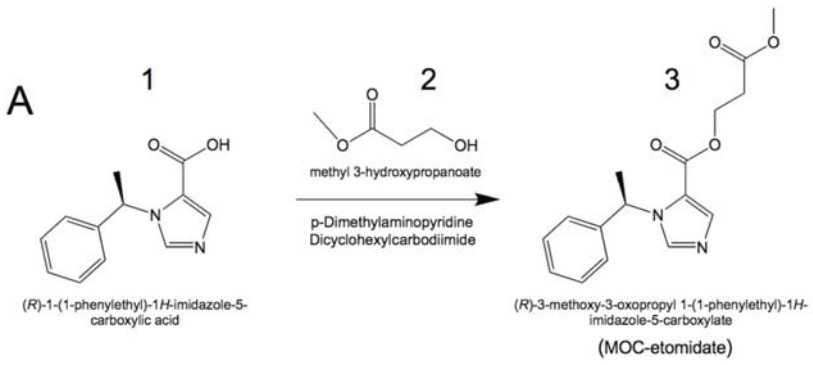
Pharmacokinetic solution

"Designer etomidate" that is more rapidly metabolised

Methoxycarbonyl-etomidate: A Novel Rapidly Metabolized and Ultra-Short Acting Etomidate Analogue That Does Not Produce Prolonged Adrenocortical Suppression

Anesthesiology. 2009 August ; 111(2): 240–249

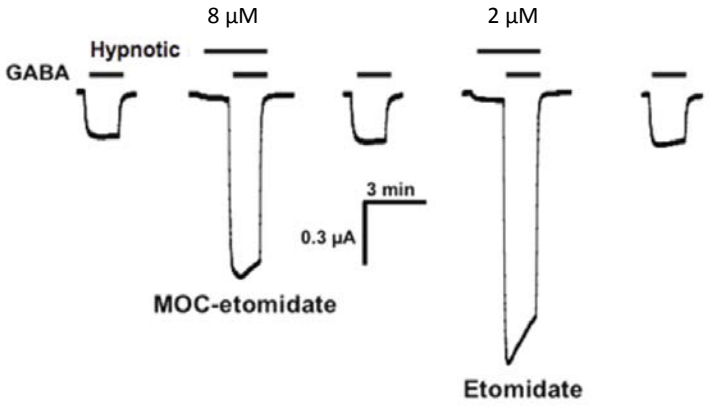
Joseph F. Cotten, M.D., Ph.D[*], S. Shaukat Husain, D.Phil.[†], Stuart A. Forman, M.D., Ph.D[‡], Keith W. Miller, D.Phil.[§], Elizabeth W. Kelly, B.A.[||], Hieu H. Nguyen, B.A.[||], and Douglas E. Raines, M.D.[‡]



Methoxy-carbonyl group designed to undergo rapid hydrolysis by esterases

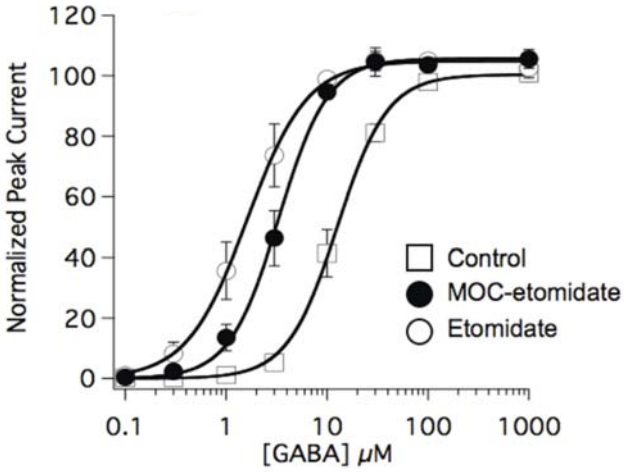
MOC-etomidate

Does it potentiate $GABA_A$ receptors ?



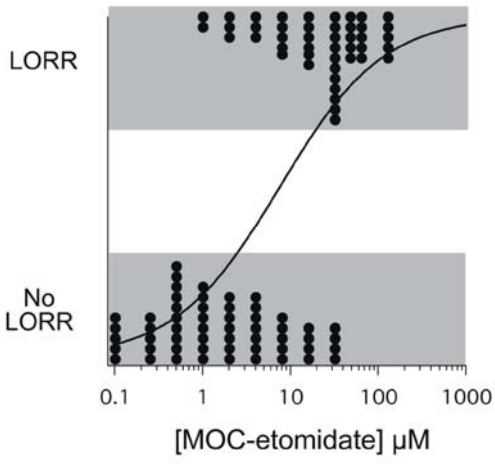
MOC-etomidate

Does it potentiate $GABA_A$ receptors ?



MOC-etomidate

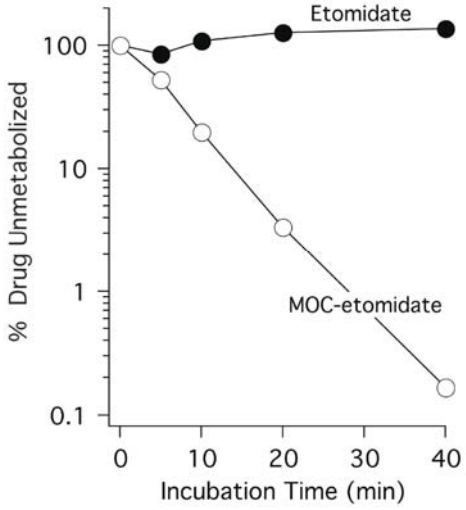
Is it an anaesthetic ?



EC_{50} = 8 ± 2 μM

MOC-etomidate

Is it metabolised more rapidly than etomidate ?

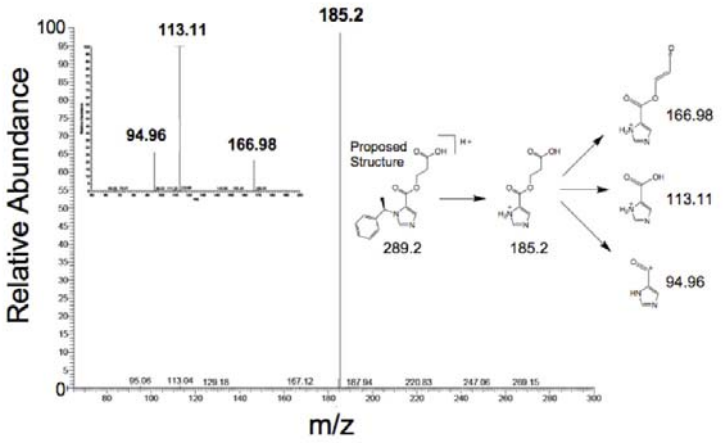


assay using human liver S9 fraction

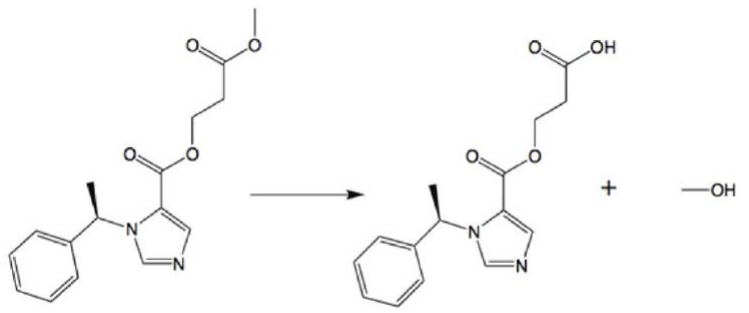
Tissue homogenate used to study metabolism *in vitro*

Metabolic half-life 4.4 minutes

Identification of metabolites using MS

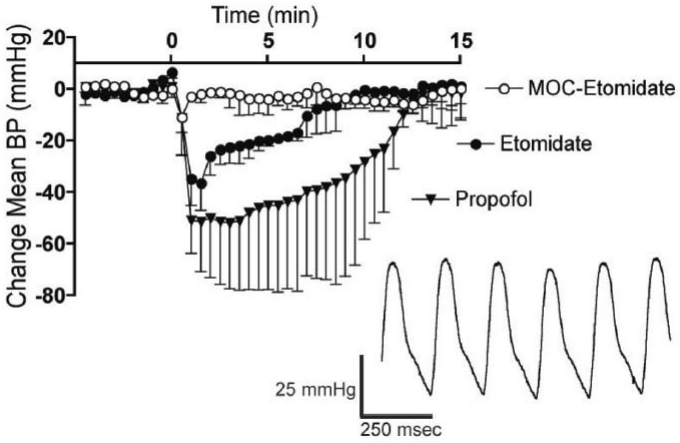


Identification of metabolic pathway

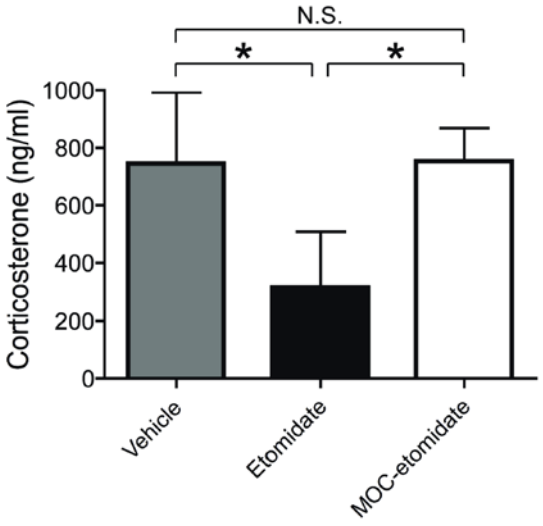


MOC-etomidate

Haemodynamic stability (rats)



Suppression of adrenal function ?



Dose 2 x ED_{50} given to rats

Measurement 30 min later

Pharmacodymamic solution

"Designer etomidate" that doesn't inhibit 11β-hydoxylase

Carboetomidate: A Pyrrole Analogue of Etomidate Designed Not To Suppress Adrenocortical Function

Anesthesiology. 2010 March ; 112(3): 637–644.

Joseph F. Cotten, M.D. Ph.D.[*], Stuart A. Forman, M.D. Ph.D.[‡], Joydev K. Laha, Ph.D.[π], Gregory D. Cuny, Ph.D.[≠], S. Shaukat Husain, D.Phil.[†], Keith W. Miller, D.Phil.[§], Hieu H. Nguyen, B.S.[||], Elizabeth W. Kelly, B.A[¥], Deirdre Stewart, Ph.D.[¶], Aiping Liu, Ph.D.[Ω], and Douglas E. Raines, M.D.[‡]

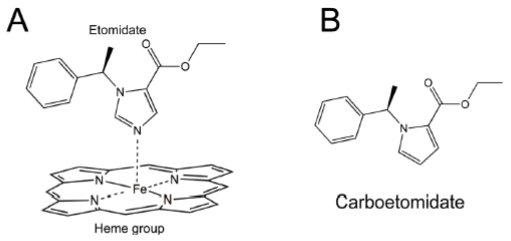
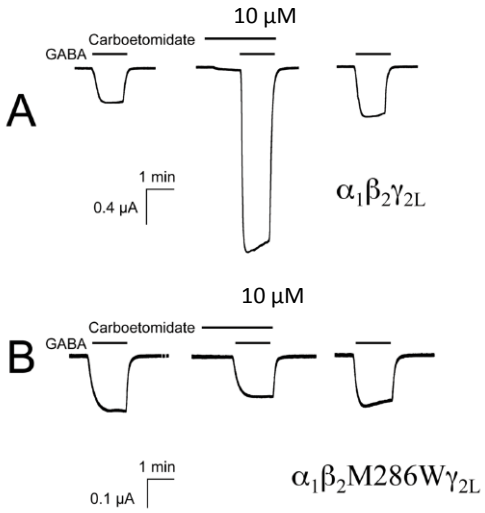


Figure 1.
(A) Hypothesized attractive interaction between the basic nitrogen in etomidate's imidazole ring and the heme iron at 11β-hydroxylase's active site. (B) Structure of carboetomidate.

Carbo-etomidate

Does it potentiate $GABA_A$ receptors ?



Carbo-etomidate

Is it an anaesthetic ?

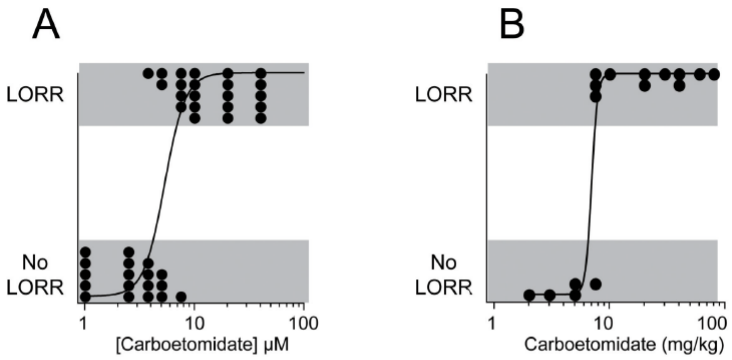
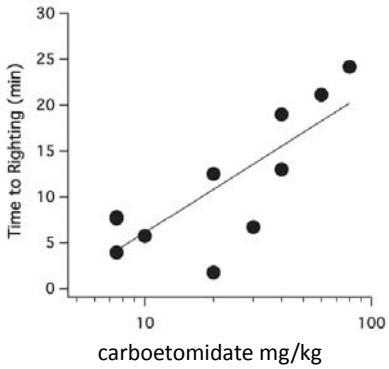
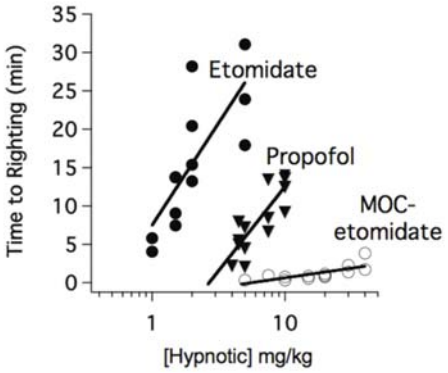


Figure 2.
(A) Carboetomidate concentration-response curve for loss of righting reflex (LORR) in tadpoles. Each data point represents the result from a single tadpole. The curve is a fit of the data set using the method of Waud [26] yielding an EC_{50} of 5.4 ± 0.5 µM. (B) Carboetomidate dose-response curve for LORR in rats. Each data point represents the results from a single rat. The curve is a fit of the data set using the method of Waud [26] yielding an ED_{50} of 7 ± 2 mg/kg.

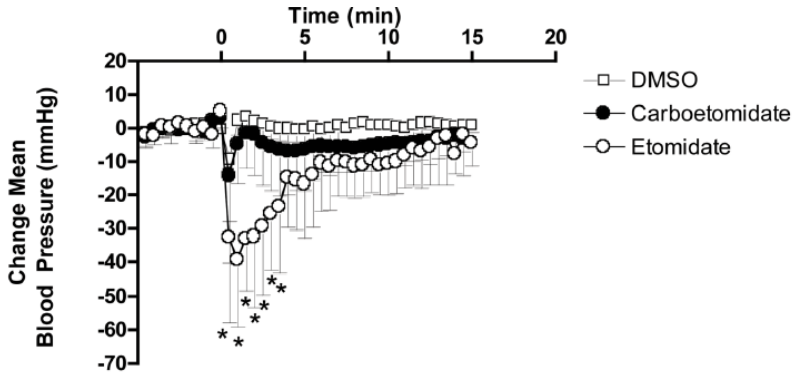
Recovery of righting reflex





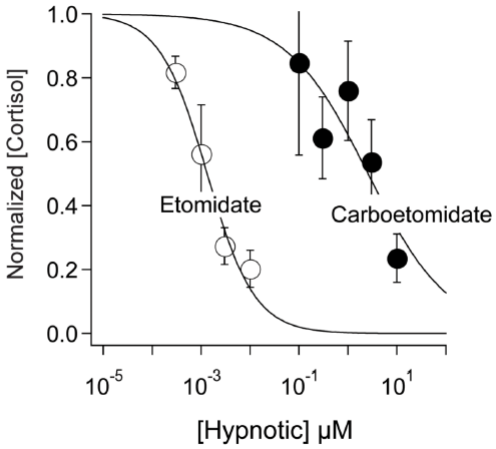
carboetomidate

Haemodynamic stability (rats)



Suppression of cortisol synthesis?

Inhibition of cortisol synthesis in human adrenocortical carcinoma cells



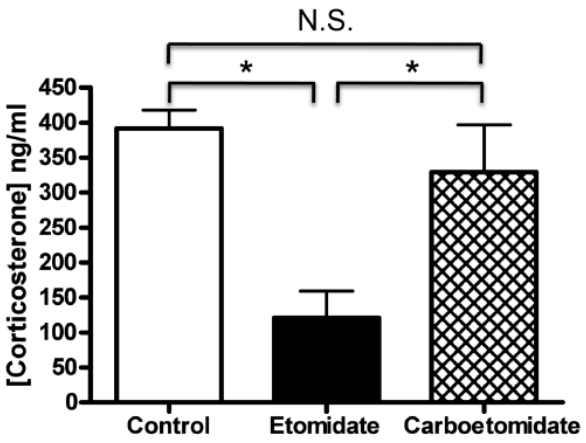
etomidate
IC_{50} = 1.3 ± 0.2 nM

carboetomidate
IC_{50} = 2.6 ± 1.5 µM

Carboetomidate is 2000 times less potent at inhibition of 11β-hydroxylase

What was the difference in anaesthetic potency ?

Suppression of adrenal function ?



Dose 2 x ED_{50} given to rats

Measurement 15 min later

Principles of Pharmacodynamics & Pharmacokinetics

Pharmacodynamics & Pharmacokinetics can be fun !