David S. Warner, M.D., Editor

Clinical and Molecular Pharmacology of Etomidate

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ABSTRACT

This review focuses on the unique clinical and molecular pharmacologic features of etomidate. Among general anesthesia induction drugs, etomidate is the only imidazole, and it has the most favorable therapeutic index for single-bolus administration. It also produces a unique toxicity among anesthetic drugs: inhibition of adrenal steroid synthesis that far outlasts its hypnotic action and that may reduce survival of critically ill patients. The major molecular targets mediating anesthetic effects of etomidate in the central nervous system are specific γ-aminobutyric acid type A receptor subtypes. Amino acids forming etomidate binding sites have been identified in transmembrane domains of these proteins. Etomidate binding site structure models for the main enzyme mediating etomidate adrenotoxicity have also been developed. Based on this deepening understanding of molecular targets and actions, new etomidate derivatives are being investigated as potentially improved sedative–hypnotics or for use as highly selective inhibitors of adrenal steroid synthesis.

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ETOMIDATE [*R*-1-(1-ethylphenyl)imidazole-5-ethyl ester] (fig. 1) is a unique drug used for induction of general anesthesia and sedation. The first report on etomidate was published in 1965 as one of several dozen aryl alkyl imidazole-5-carboxylate esters[1] synthesized by Janssen Pharmaceuticals (a division of Ortho-McNeil-Jannsen Pharmaceuticals, Titusville, NJ). Initially developed as antifungal agents, the potent hypnotic activity of several compounds was observed during animal testing; and several compounds, including etomidate, appeared significantly safer than barbiturates.

Etomidate contains a chiral carbon (fig. 1). Initial studies of racemic etomidate in rats demonstrated lethality at approximately 12 times its effective hypnotic dose (median lethal dose/ED_{50}, approximately 12) compared with barbiturates with median lethal dose/ED_{50} ratios (therapeutic indexes) of 3–5.[1] Subsequent studies[2,3] found that the isolated *R*(+)-enantiomer of etomidate has 10- to 20-fold greater hypnotic potency than *S*(−)-etomidate. The median lethal dose/ED_{50} ratio for *R*(+)-etomidate is 26 in rats,[4] significantly higher than therapeutic indexes for other general anesthetics (table 1). Preclinical experiments in mammals also demonstrated that etomidate injection was associated with minimal hemodynamic changes or respiratory depression, features that were presumed to result in its unusually favorable safety profile.[5]

Etomidate was introduced into clinical practice in 1972, and initial reports of its use in humans emerged in the clinical literature soon afterward.[6,7] Academic publications focusing on etomidate increased steadily until 1983, when the number of reports rapidly doubled after discovery of its adrenal toxicity (fig. 2). Subsequently, the number of yearly published articles focusing on etomidate diminished (apparently in parallel with its use in operating rooms), but this rate has resurged in the past decade. Renewed interest in etomidate parallels its widening use during intubations in emergency departments and intensive care units, and new concerns exist about the impact of etomidate-induced adrenal toxicity in critically ill patients. The recent increase in publications on etomidate also reflects scientific progress in understanding this drug's molecular pharmacologic features.

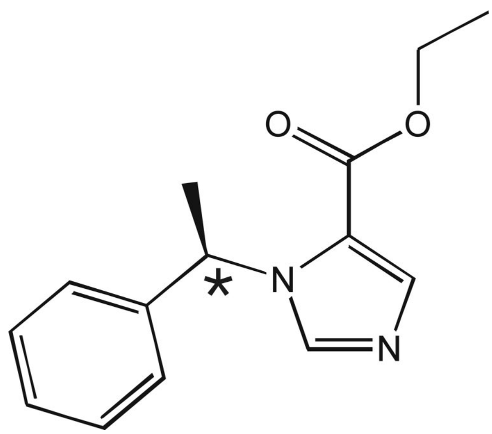

Fig. 1. Chemical structure of etomidate. Critical structural features for anesthetic activity include a single methylene group between the imidazole and phenyl group and the *R*(+) configuration at the chiral center (labeled with an *asterisk*).

Clinical Pharmacology

Formulation and Dosing

Etomidate formulations for clinical use contain the purified *R*(+)-enantiomer. Etomidate has a pK_a of 4.2 and is hydrophobic at physiologic pH. To increase solubility, it is formulated as a 0.2% solution either in 35% propylene glycol (Amidate; Hospira, Inc, Lake Forest, IL) or lipid emulsion (Etomidate-Lipuro; B. Braun, Melsungen, Germany).[8] Formulations in cyclodextrins have also been developed.[9,10]

Early clinical studies determined that intravenous bolus doses of 0.2–0.4 mg/kg provided hypnosis for 5–10 min. After a bolus, maintenance of general anesthesia can be achieved by continuous infusion of etomidate at 30–100 $\mu g \cdot kg^{-1} \cdot min^{-1}$.[11-13] Oral transmucosal etomidate has been used to induce sedation,[14] and rectal administration has been used to induce general anesthesia in pediatric patients.[15]

Table 1. Acute Toxicity Ratios of Intravenous Anesthetic Induction Drugs

Anesthetic Induction Drug	Acute Toxicity Ratio, LD50/ED50*
R(+)-etomidate	26[5]
Althesin (alphaxalone/alphadolone)	17.3[158]
Ketamine (racemic)†	6.3[159]
Methohexital	4.8-9.5[5,158]
Thiopental	3.6-4.6[5,158,160]
Pentobarbital	3.4[160]
Propofol	3.4[158]

* Data are from therapeutic index studies in mice and rats using intravenous injection. † The therapeutic index of (+)-ketamine is 10, whereas that of the (−) enantiomer is 4.0.

ED50 = dose that is pharmacologically effective to 50% of the experimental population; LD50 = the dose resulting in 50% mortality within 24 h.

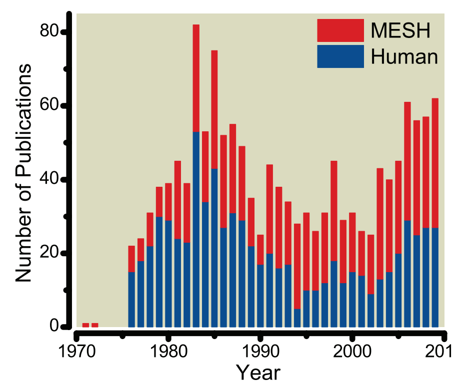

Fig. 2. Etomidate publications in PubMed. The graph displays numbers of publications within a calendar year, based on PubMed searches with *etomidate* as a Medical Subject Headings term (sum of *red* plus *blue bars*) or the subset of these publications with humans as the subjects (*blue bars* only). Data are inclusive through December 2009.

Systemic Effects

Etomidate does not inhibit sympathetic tone or myocardial function,[16,17] and typical anesthetic induction doses produce minimal blood pressure and heart rate changes in patients, including those with valvular or ischemic heart disease.[12,18-20] For the same reason, etomidate does not block sympathetic responses to laryngoscopy and intubation; these responses are often blunted by premedication with opioids.[21,22] Etomidate produces less apnea than barbiturates or propofol, no histamine release, and rare allergic reactions. Because of its remarkably benign hemodynamic effects, etomidate has proved useful for general anesthetic induction in patients undergoing cardiac surgery and in those with poor cardiac function.[23]

Etomidate also provides advantages for induction of anesthesia in the setting of hemorrhagic shock. In a pig model of hemorrhagic shock, the pharmacodynamics and pharmacokinetics of etomidate are minimally altered,[24] in contrast to other anesthetic drugs.[25,26] As a result of its favorable profile for anesthetic induction in a variety of critically ill patients, etomidate has been adopted by many emergency medicine physicians as the hypnotic drug of choice for rapid-sequence induction and intubation.[27-29]

Hepatic blood flow is modestly reduced after induction of general anesthesia with etomidate, but this has minimal impact on pharmacokinetics and metabolism of anesthetic agents.[30,31] Cerebral blood flow is reduced, along with cerebral metabolic rate and intracranial pressure, whereas cerebral perfusion pressure is maintained or increased during etomidate-induced anesthesia.[32-34] Electroencephalographic changes during hypnosis with etomidate are similar to those seen with barbiturates.[35] Bispectral index monitor values decrease after etomidate bolus administration and return to baseline during recovery of consciousness.[36] During brief etomidate infusions, bispectral index values correlate well with sedation scores.[37] Etomidate increases latency and decreases amplitude of auditory evoked potentials.[38] The du-

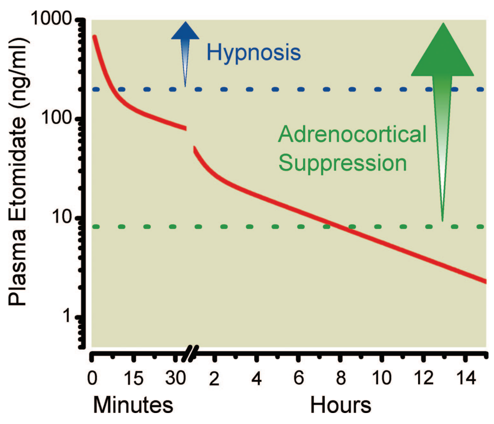

Fig. 3. Single intravenous bolus pharmacokinetics of etomidate. The etomidate plasma concentration after a single intravenous bolus (3 mg/kg) is depicted on a semilogarithmic plot with the early decline period expanded. This concentration *versus* time profile is based on pharmacokinetic parameters determined by Van Hamme *et al.*,[30] showing three distinct decline phases with half-times of 2 min, 21 min, and 3.9 h. *Colored dashed lines* indicate approximate threshold etomidate plasma concentrations associated with hypnosis (*blue line* at 200 ng/ml) and adrenocortical suppression (*green line* at 8 ng/ml). Together, these data illustrate why the duration of hypnosis (approximately 8 min) is much shorter than the duration of adrenocortical suppression (approximately 8 h) after a single etomidate dose.

ration of epileptiform activity after electroconvulsive therapy is longer after anesthetic induction with etomidate *versus* methohexital or propofol.[39] Somatosensory evoked potential amplitudes are enhanced by etomidate,[40] and motor evoked potential amplitudes are suppressed less by etomidate than propofol, thiopental, or methohexital.[41]

Pharmacokinetics and Metabolism

In healthy patients, etomidate is approximately 75% protein bound.[42] Etomidate is characterized by a large central volume of distribution, 4.5 l/kg, and a large peripheral volume of distribution, 74.9 l/kg, because of its high solubility in fat.[30,37,43] The single-bolus pharmacokinetic profile of plasma etomidate concentration is described by a three-compartment model (fig. 3).[30] The fast, intermediate, and slow declines in plasma etomidate are thought to correspond to distribution into highly perfused tissues, redistribution into peripheral tissues (mostly muscle), and terminal metabolism, respectively. The hypnotic effect of an intravenous bolus of 3 mg/kg etomidate terminates as redistribution into the peripheral compartment starts to dominate the plasma concentration profile. Etomidate metabolism in laboratory animals and humans depends on hepatic esterase activity, which hydrolyzes the drug to a carboxylic acid and an ethanol-leaving group.[44] The carboxylate metabolite is excreted mostly in urine and to a lesser degree in bile. Total plasma clearance is 15–20 $ml \cdot kg^{-1} \cdot min^{-1}$, and the terminal metabolic half-life of etomidate in humans ranges from 2 to 5 h. Elderly or ill patients often require decreased etomidate doses because of reduced protein binding and reduced clearance.[42,45,46] The pharmacokinetic parameters for etomidate indicate its suitability for use as a continuous infusion, with a context-sensitive half-time shorter than that of propofol.[47] Prolonged etomidate infusion for anesthesia and sedation was practiced during the first decade of clinical availability.[32,48-52] Other considerations (adrenal toxicity) preclude this application. (The Adrenal Toxicity, Sepsis, and Exogenous Steroids section provides further details.)

Adverse Effects

Several unfavorable effects associated with etomidate were noted in early studies, including pain on injection and myoclonic movements during induction of general anesthesia.[53-55] Pain on injection was worse with etomidate in aqueous solutions compared with the formulation in 35% propylene glycol.[56] Formulation into medium chain-length lipids or cyclodextrins appears to decrease the incidence of injection pain and hemolysis further.[9,57] The incidence of myoclonus increases with etomidate dose and can be attenuated by split-dose induction[58] or premedication with benzodiazepines,[59] thiopental, dexmedetomidine,[60] and/or opioids.[22,61,62]

Postoperative nausea and vomiting are cited as frequent adverse effects of etomidate, but few studies have formally compared postoperative nausea and vomiting after etomidate *versus* other agents used for induction of general anesthesia. Early investigators reported that the incidence of postoperative nausea and vomiting after induction with etomidate is approximately 40%,[50,55] comparable with that after barbiturates,[43,56] and higher than that after propofol.[63] More recently, the reported incidence of nausea after induction with etomidate in lipid emulsion was similar to that associated with propofol,[64,65] whereas the incidence of vomiting was higher with etomidate.[65]

Adrenal Toxicity, Sepsis, and Exogenous Steroids

Adrenal cortical inhibition by etomidate has received much attention and significantly limits its use as both an anesthetic and a sedative. Nevertheless, the effect of etomidate on clinical outcomes has never been carefully studied in a large population of surgical or intensive care patients.

1n 1983, a decade after its introduction into clinical use, Ledingham and Watt[66] reported retrospective data showing increased mortality among intensive care patients receiving prolonged etomidate infusions for sedation compared with patients receiving benzodiazepines (69% *vs.* 25%).[67] Soon afterward, McKee and Finlay[68] reported that cortisol replacement therapy could reduce the mortality in a similar group of critically ill patients receiving etomidate infusions. At that time, there was emerging preclinical evidence that etomidate suppressed adrenocortical function in rats,[69] and clinical investigators[70,71] rapidly confirmed this toxicity in patients. Etomidate suppressed normal cortisol and aldosterone increases after surgery and adrenal responses to corticotrophin. Adrenal suppression lasted 6–8 h in patients after a single-induction dose of etomidate[72,73] and more than 24 h after etomidate infusion.[74]

The clinical community reacted to revelations about adrenal toxicity by ceasing the use of etomidate for long-term infusions. Some editorials[75,76] recommended halting its use altogether, whereas others suggested that etomidate had value as a single-dose induction drug for selected patients.[77] The drug package insert was amended to state that etomidate use is approved for induction of general anesthesia and anesthetic maintenance for short operative procedures. It specifically warns against administration by prolonged infusion.

Subsequent research[78] showed that etomidate is far more potent as an inhibitor of steroid synthesis than as a sedative–hypnotic agent. Etomidate plasma concentrations associated with hypnosis in patients are higher than 200 ng/ml (1 μM), whereas concentrations less than 10 ng/ml are associated with adrenal cortical suppression.[72] The *in vitro* IC_{50} for etomidate inhibition of cortisol synthesis in cultured adrenal cells is 1 nM, which closely matches the apparent dissociation constant for etomidate binding to membranes of these cells.[79] Together, the disparate etomidate concentration dependence values for hypnosis *versus* adrenotoxicity and multiphase pharmacokinetics account for the dramatic difference in the durations of these two actions after a single intravenous bolus (fig. 3).[72]

Recently, concern about etomidate-induced adrenal toxicity in critically ill patients and the use of corticosteroids to treat this effect has reemerged. Exposure to single-dose etomidate was a confounding variable in a large multicenter trial evaluating the use of supplemental corticosteroids in septic patients with and without adrenal insufficiency.[80] Enrollment in this study was from September 1995 to March 1999; in July 1996, inclusion criteria were altered to exclude patients who had received etomidate within 6 h. At that point, 72 enrollees had received etomidate, and 68 of these individuals were nonresponders to corticotrophin.[81] Thus, at least 30% of the nonresponders in this study (229 in total) had received etomidate; it is likely that additional patients received etomidate between 6 and 24 h before enrollment. In a 500-patient follow-up study of low-dose corticosteroid therapy of septic shock (CORTICUS),[82] etomidate was administered to 20% of patients before enrollment and 8% of patients after enrollment. Although etomidate was given on average 14 h before testing for adrenal insufficiency, it was associated with a 60% nonresponse rate to corticotrophin, significantly higher than that of enrollees who did not receive etomidate. Similar results have been reported by others.[83] The CORTICUS study[82] concluded that supplemental steroids did not improve the long-term outcome of septic shock patients with adrenal insufficiency. Retrospective analyses of the CORTICUS cohort suggest that patients receiving etomidate before enrollment had a 28-day mortality significantly higher than other patients in the trial and that steroids provided no benefit to those who received etomidate.[82,84,85]

Other studies of patients with sepsis and trauma have examined the duration of adrenal insufficiency after single-dose etomidate and its effect on outcomes. In this population, the duration of adrenal suppression after a single dose of etomidate is longer than 24 h[87,88] and may last up to 72 h.[86] However, the impact of single-dose etomidate on outcomes in critically ill patients remains unclear. Hildreth *et al.*[89] reported that trauma patients randomized to intubation using etomidate had longer hospital and intensive care unit lengths of stay than a group intubated using fentanyl and midazolam. In contrast to these and the CORTICUS study results, a nonrandomized study by Tekwani *et al.*[90] found no difference in mortality among septic patients who received etomidate for intubation in the emergency department *versus* those who received other agents. Ray and McKeown[91] also found no evidence of excess mortality associated with etomidate in a retrospective study. A recent randomized controlled trial[92] comparing etomidate with ketamine for intubation of critically ill, mostly nonseptic, patients also found no difference in mortality. Clearly, large well-designed trials are needed to define the clinical impact of single-dose etomidate in critically ill patients. Meanwhile, a vigorous debate about the use of etomidate for intubation of these patients continues.[93,94]

Molecular Pharmacologic Features

There are fewer clinical studies focusing on etomidate than on either propofol or isoflurane†, yet the molecular pharmacologic features of etomidate are understood far better than other intravenous or inhaled general anesthetics. Etomidate appears to produce hypnosis, amnesia, and inhibition of nociceptive responses, almost exclusively *via* actions at one class of neuronal ion channels (*i.e.*, γ-aminobutyric acid type A receptors [$GABA_A$ receptors]).[95,96] Molecular targets mediating adrenal steroid inhibition and pain on injection have also been identified.

$GABA_A$ Receptors: Mediators of Etomidate Anesthesia

Soon after etomidate became available for clinical use, it was noted to produce effects similar to the endogenous neurotransmitter GABA in the nervous system.[97] Indeed, it is firmly established that the molecular targets underlying the anesthetic actions of etomidate are $GABA_A$ receptors, which are the major inhibitory neurotransmitter receptors in mammalian brains.[98] $GABA_A$ receptors are neurotransmitter-activated ion channels that selectively conduct chloride ions. Under normal conditions, their activation stabilizes neuronal membrane voltage near the chloride Nernst potential of −70 mV. $GABA_A$ receptors are members of the superfamily of Cys loop ligand-gated ion channels that includes nicotinic acetylcholine receptors from muscle and nerve, glycine receptors, and serotonin type 3A receptors. All of these receptors are structurally similar and are formed from five polypeptide subunits surrounding an ion-conductive transmembrane channel. All Cys loop receptor subunits consist of a large amino-terminal extracellular domain, four

† A PubMed search strategy with the name of the anesthetic drug in the title of the publication and "human" as a Medical Subject Headings term identified 734 articles on etomidate, 4,968 on propofol, and 1,841 on isoflurane.

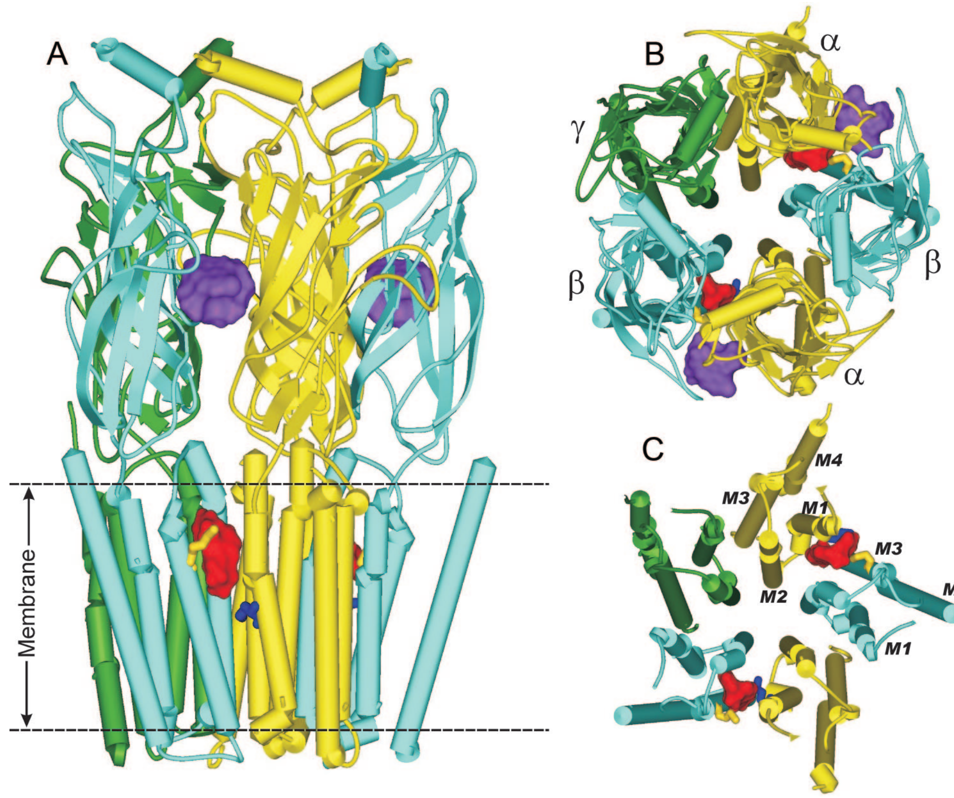

Fig. 4. Molecular structure of $GABA_A$ receptors. A $GABA_A$ receptor homology model, based on the structure of *Torpedo* nicotinic acetylcholine receptors, is shown in two views. The subunits are color coded: α, *yellow*; β, *blue*; γ, *green*. (*A*) The receptor is depicted in a membrane cross-sectional view, showing the extracellular domains containing GABA binding sites (*purple*) and the transmembrane domains forming the etomidate sites (*red*) between α and β subunits. Two amino acid residues, αM236 (*blue*) and βM286 (*yellow*), are shown adjacent to the etomidate binding site. The intracellular domains between M3 and M4 are not shown; their structures remain undefined. (*B*) The pentameric model is depicted as viewed from the extracellular space with subunits labeled. The ion channel is formed by the M2 domains at the center of the subunits. (*C*) The transmembrane domains are depicted with the extracellular domains removed. Transmembrane domains of one α subunit are labeled. (This figure was kindly provided by David Chiara, M.D., Ph.D., Department of Neurobiology, Harvard Medical School, Boston, Massachusetts.)

hydrophobic transmembrane domains (M1 through M4), and a large intracellular domain between M3 and M4. Structural models of $GABA_A$ receptors (fig. 4A–C) are based on high-resolution studies of crystallized acetylcholine-binding protein from snail synapses, homologous to extracellular domains,[99] *Torpedo* nicotinic acetylcholine receptors,[100] and crystallized pentameric prokaryotic channels.[101-103]

Eighteen distinct $GABA_A$ receptor subunits are encoded in the human genome,[104] but only approximately a dozen subunit combinations form neuronal channels. Most of these consist of two α subunits, two β subunits, and one γ subunit arranged γ-β-α-β-α counterclockwise when viewed from the extracellular space.[105] Heterologously expressed receptors containing α1, β2, and γ2 subunits display GABA sensitivity, drug sensitivity, and open-closed transition rates similar to synaptic $GABA_A$ receptors in the brain.[106] Synaptic GABA concentrations are thought to briefly reach several millimolar and to decay within milliseconds because of uptake *via* GABA transporters. Postsynaptic $GABA_A$ receptor channels open within a millisecond, generating an inhibitory postsynaptic current, which deactivates over tens of milliseconds, far longer than GABA remains in the synapse.[107] During an inhibitory postsynaptic current, action potential generation is impaired in the postsynaptic neuron; therefore, current deactivation is thought to be a factor in regulating the frequency response of neuronal circuits.[108,109] Some $GABA_A$ receptors, formed from α and β subunits in combination with δ or ε subunits, are expressed on neuronal cell bodies and axons.[110] These extrasynaptic receptors produce small tonic chloride "leak" currents in response to low micromolar concentrations of GABA in the extrasynaptic space.[111,112]

Etomidate Actions at $GABA_A$ Receptors

Two effects on $GABA_A$ receptors, produced by different concentrations of etomidate, have been described. At concentrations associated with clinical doses, etomidate positively modulates $GABA_A$ receptor activation by agonists.[98] In other words, when etomidate is present, $GABA_A$ receptors are activated by concentrations of GABA lower than required under normal conditions.[2,113,114] Clinical concentrations of etomidate also slow the inhibitory postsynaptic current decay mediated by synaptic $GABA_A$ receptors,[115,116] prolonging postsynaptic inhibition and reducing the frequency response of neuronal circuits. Enhanced activation of extrasynaptic receptors is also observed at clinical etomidate concentrations, increasing the tonic inhibitory "leak" current and reducing neuronal excitability. Yang and Uchida[115] noted that etomidate effects on tonic currents mediated by extrasynaptic $GABA_A$ receptors may be more important than effects on synaptic currents. Etomidate at supraclinical concentrations also directly activates synaptic $GABA_A$ receptor channels in the absence of GABA, an action variously termed direct activation, GABA-mimetic activity, or allosteric agonism.[2,114,115,117]

Both positive modulation of GABA-mediated activity and direct activation of $GABA_A$ receptors display parallel dependences on drug and receptor structures. For both etomidate actions, stereoselectivity for the *R*(+)-enantiomer is of the same magnitude (10- to 20-fold) seen in animal studies of hypnotic and antinociceptive activity.[2,114,118,119] Both etomidate actions also show similar dependence on $GABA_A$ receptor subunit makeup. Receptors containing β2 and/or β3 subunits are modulated and activated by etomidate, whereas those containing β1 are much less sensitive to both etomidate actions.[113,117,120] Etomidate sensitivity is also affected by the presence of a γ subunit[113] and weakly by the α subtype.[117]

These parallels suggest that a single class of etomidate sites on $GABA_A$ receptors mediates both modulation of GABA activation and direct activation. Indeed, both of these effects in $\alpha1\beta2\gamma2L$ receptors can be quantitatively modeled with an equilibrium Monod–Wyman–Changeux allosteric coagonist mechanism, by which etomidate binding to its sites is determined by whether the receptor is in one of two canonical states: open *versus* closed (fig. 5).[114] In essence, etomidate binds weakly (K_E, approximately 35 μM) to closed receptors but tightly (K_E*, approximately 0.27 μM) to open receptors; therefore, the drug stabilizes open states whether GABA is bound or not bound. This class of model was optimal with two equivalent etomidate sites.

Mutations That Alter Etomidate Sensitivity of $GABA_A$ Receptors

A β subunit region containing the M2 domain influences the differential etomidate sensitivity of $GABA_A$ receptors containing β1 *versus* β2 subunits.[121] The only amino acid in M2 that differs between β1 and β2 is at position 265 of the mature protein. β265 is a serine (S) in β1 and an asparagine (N) in β2 and β3. A point mutation replacing β1S265 with N (β1S265N) increases etomidate sensitivity, whereas replacing β2 or β3N265 with S (β2/3N265S) dramatically reduces etomidate sensitivity.[121] Similarly, an anesthetic-insensitive mutant *Drosophila melangaster* (fruit fly) line contains a methionine (M) at the homologous amino acid in M2, instead of the N found in the wild type. A mutation from N265 to M in the β2 or β3 subunit of mammalian $GABA_A$ receptors also confers

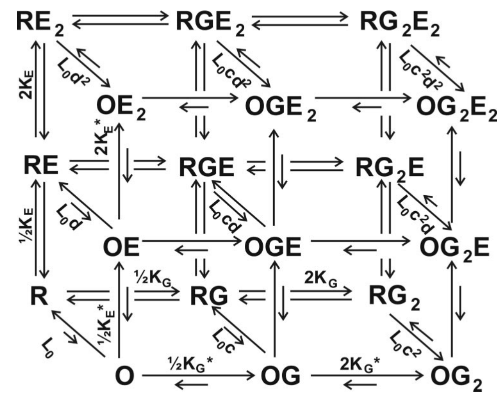

Fig. 5. Monod–Wyman–Changeux two-state equilibrium model for etomidate and GABA activation of $GABA_A$ receptors. The scheme depicts allosteric coagonism for $GABA_A$ receptors with two equivalent GABA (*G*; orthosteric agonist) sites and two equivalent etomidate (*E*; allosteric agonist) sites. The L_0 parameter describes the basal equilibrium between the two canonical states: inactive (*R*) and active (*O*). K_G is the dissociation constant for GABA interactions with *R*-state receptors; and K_G* is the dissociation constant for GABA interactions with *O*-state receptors. The GABA efficacy factor, *c*, is defined as K_G*/K_G. K_E is the dissociation constant for etomidate interactions with *R*-state receptors; and K_E* is the dissociation constant for etomidate interactions with *O*-state receptors. The etomidate efficacy factor, *d*, is defined as K_E*/K_E. The differently sized *arrows* illustrate how equilibria shift as ligands bind and functional state changes.

insensitivity to etomidate.[122-124] Mutations at βN265 produce parallel changes in etomidate modulation of GABA-activated receptor-mediated currents and direct activation of channels. Quantitative electrophysiologic analysis of $GABA_A$ receptors containing both β2N265S and β2N265M mutations show little impact on basal or GABA-mediated activation and different degrees of reduced etomidate sensitivity.[125] The β2N265M mutation totally eliminates etomidate sensitivity, whereas the β2N265S mutation reduces etomidate-induced shifts in GABA EC_{50} (EC_{50} ratio) more than 8-fold relative to the wild type (table 2).

All $GABA_A$ receptor β subunits contain a methionine at position 286 in their M3 domains, and βM286 mutations also influence etomidate sensitivity. The βM286W mutation eliminates etomidate modulation of receptors, whereas the homologous αA291W mutation has no effect on etomidate actions.[123,124,126] Quantitative electrophysiologic analysis demonstrates that $GABA_A$ receptors containing the β2M286W mutation display both enhanced sensitivity to GABA and spontaneous activity, effects that mimic the actions of etomidate on wild-type channels (table 2).[127]

Etomidate Anesthesia in Transgenic Animals

Mutations at β2N265 and β3N265 have been incorporated into transgenic "knock-in" mice to test the role of these subunits in anesthetic actions. Jurd *et al.*[128] reported that β3N265M knock-in animals have grossly normal morphological and behavioral phenotypes but are resistant to both loss of righting

Table 2. GABA$_A$ Receptor Mutant Effects on GABA and Etomidate Sensitivity*

Receptor	Spontaneous Activation†	GABA EC$_{50}$ (μM)‡	GABA Efficacy§	Etomidate EC$_{50}$ (μM)‡	Etomidate Efficacy§	Left-shift Ratio (CNTL/ETO)‖
α1β2γ2L	<0.001	26	0.9	36	0.4	20
α1M236Wβ2γ2L	0.16	2.0	0.99	12	0.97	1.7
α1β2M286Wγ2L	0.04	6.6	1.0	NA	<0.001	1.1
α1β2N265Sγ2L	<0.001	27	0.93	78	0.03	2.3
α1β2N265Mγ2L	<0.001	32	0.84	NA	<0.001	0.95

* All functional effects are estimated from voltage–clamp electrophysiological experiments on receptors expressed in *Xenopus oocytes*. † Spontaneous activation is a measure of the propensity of channels to open in the absence of agonist and other ligands. It is estimated using a potent channel blocker (picrotoxin) that inhibits the spontaneously active receptors. The picrotoxin-sensitive current is reported as a fraction of maximum GABA current. ‡ GABA EC$_{50}$ is the GABA concentration eliciting half-maximal activation of receptors. Etomidate EC$_{50}$ is defined similarly for etomidate's direct activating (agonist) activity. § GABA's efficacy is an estimate of the fraction of receptors activated when all agonist sites are occupied by GABA. It is estimated using positive allosteric modulators to enhance the maximum current elicited by high GABA concentrations. We assume that the combination of high GABA plus allosteric enhancer activates all receptors. Etomidate's efficacy is the maximum current elicited by etomidate, normalized to the maximum current elicited by GABA. ‖ The left-shift ratio is a measure of etomidate modulation of GABA responses. It is calculated as the ratio of GABA EC$_{50}$ values in the absence of etomidate to that in the presence of 3.2 μM etomidate. A large ratio indicates sensitivity to etomidate modulation, whereas a ratio of 1.0 or less indicates no positive modulation.

CNTL = control; ETO = etomidate.

reflexes and antinociceptive (immobilizing) actions of etomidate and propofol at doses higher than those affecting 100% of wild-type animals. Reynolds *et al.*[129] developed β2N265S knock-in mice and reported that they also have normal morphological features and behavior, including sleep and electroencephalographic activity. The β2N265S knock-in mice show normal sensitivity to etomidate for loss of righting reflexes and antinociceptive actions, but these mice are resistant to sedative and hypothermic actions of etomidate.[129,130] Etomidate enhancement of tonic currents associated with extrasynaptic receptors is lost in neurons from β2N265S transgenic mice.[131] Further evidence implicating extrasynaptic receptors derives from knock-out mice lacking GABA$_A$ receptor α5 subunits, which are insensitive to the amnestic effects of etomidate.[132] However, sedative–hypnotic actions in $\alpha5^{-/-}$ animals are similar to those in wild-type littermates. Similarly, $\delta^{-/-}$ knock-out animals show normal sensitivity to etomidate hypnosis.[133] Transgenic animal studies, such as these, confirm that etomidate acts *via* GABA$_A$ receptors and that different clinical actions of etomidate are mediated by specific receptor subtypes containing different subunits. Hypnotic and immobilizing actions are mediated by receptors containing β3 subunits, whereas sedation is linked to receptors containing β2. Extrasynaptic receptors, which often contain α5 and δ subunits, appear to be linked to etomidate-induced amnesia but not to hypnosis and immobility.

Location of Etomidate Sites on GABA$_A$ Receptors

Etomidate, with its high potency and stereoselectivity, proved an excellent candidate for creating photoreactive derivatives that covalently modify target channels. Husain *et al.*[3] synthesized a diaziryl derivative, azietomidate; and Bright *et al.*[134] produced an azide. These photolabels display stereoselectivity and pharmacologic activity almost identical to that of etomidate in both animals and GABA$_A$ receptors.[3,134,135] In the presence of ultraviolet light, azietomidate effects on GABA$_A$ receptors become irreversible.[116] Radiolabeled azietomidate was used to photolabel affinity-purified bovine GABA$_A$ receptor protein, leading to the identification of two photomodified amino acids: M236 in M1 on α subunits and M286 in M3 on β subunits.[136] The addition of etomidate blocked photoincorporation at both positions in parallel, suggesting that they contribute to the same binding pockets formed where α subunits abut β subunits (fig. 4A). Two such interfacial sites are predicted to be formed by most GABA$_A$ receptors, consistent with the predictions from functional analysis.[114]

More evidence that αM236 and βM286 are involved in etomidate binding comes from recent molecular studies of mutations at these residues. GABA$_A$ receptors with tryptophan mutations at either α1M236 or β2M286 display functional characteristics that mimic the reversible effects of etomidate on wild-type receptors.[127] Both α1M236W and β2M286W also reduce receptor sensitivity to etomidate, perhaps because the large tryptophan side chains occupy the space where etomidate binds. Cysteine mutations have been used to introduce free sulfhydryls at α1M236 and β2M286, which are accessible to modification by selective reagents.[137] Sulfhydryl modification of α1M236C or β2M286C is blocked by etomidate (Deirdre Stewart, Ph.D., Department of Anesthesia, Critical Care, and Pain Medicine, Massachusetts General Hospital, Boston; unpublished research findings; April 1, 2010), confirming that the drug binds close to both residues. The hypothesis that etomidate binds between transmembrane helices on two adjacent GABA$_A$ receptor subunits differs from previous proposals that anesthetics bind within a single subunit.[138] Recently, Bali *et al.*[137] provided further evidence that αM236 and βM286 residues of GABA$_A$ receptors are on nearby helical domains and oriented toward interfacial clefts between subunits. Their experiments showed that β2M286C forms intersubunit cross-linking disulfide bonds with cysteines substituted at two α subunit M1 domain loci on the same helical face as α1M236.

Etomidate Interactions With Adrenal Steroidogenesis Enzymes

During etomidate infusion, plasma concentrations of cortisol, cortisone, and aldosterone decrease, whereas those of 11-deoxycorticosterone, 11-deoxycortisol, progesterone, and 17-hydroxyprogesterone increase.[139] These clinical results, and related *in vitro* studies,[140] indicate that etomidate inhibits adrenal steroid synthesis primarily by blocking the activity of CYP11B1, also known as 11β-hydroxylase or P450c11. This mitochondrial cytochrome enzyme converts 11-deoxycortisol to cortisol and 11-deoxycorticosterone to corticosterone and is 95% homologous to the CYP11B2 (aldolase) enzyme in the pathway leading to aldosterone.[141]

The imidazole ring of etomidate is likely to be a major determinant of its binding to adrenal cytochrome enzymes. Many other imidazole compounds inhibit CYP11B enzymes,[142] and a variety of crystal structure studies confirm that imidazole nitrogens coordinate (form dipolar bonds with) heme irons located at the active sites of prokaryotic and eukaryotic cytochromes.[143-145] High-efficiency *in vitro* production of purified human CYP11B1 has recently been reported,[146] and high-resolution structural data for the molecule may be available in the near future. Homology models based on crystal structures of related enzymes have been developed and used for in silico ligand etomidate docking studies (fig. 6).[147]

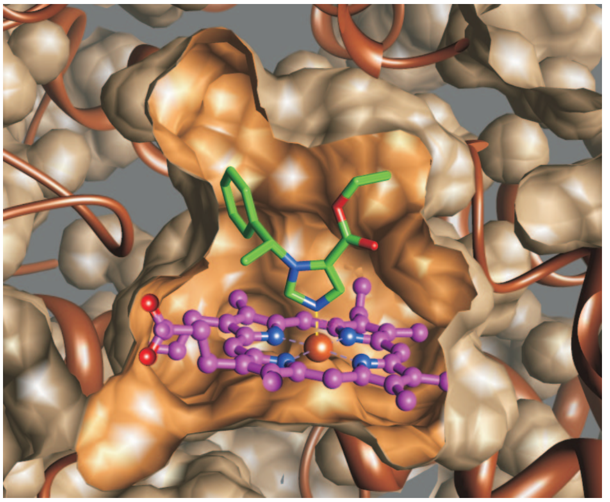

Fig. 6. Homology model for etomidate binding to CYP11B1. The binding pocket of CYP11B1 is depicted based on high-resolution crystal structures of related cytochromes.[147] Etomidate is bound within the binding pocket, oriented to form a strong coordinate bond between its free imidazole nitrogen and the heme iron of the enzyme. (This figure was kindly provided by Keith W. Miller, D. Phil., and Shunmugasundararaj Sivananthaperumal, Department of Anesthesia, Critical Care, and Pain Medicine, Massachusetts General Hospital, Boston, Massachusetts.)

Adrenergic Receptors and Cardiovascular Stability With Etomidate

α-2 Adrenergic receptors are activated by etomidate, but this action is unrelated to its hypnotic effects in mice.[148] However, the transient hypertension produced by etomidate in wild-type mice is absent in knockout mice lacking either α2B or α2A adrenergic receptor subtypes. This result indicates that α2 adrenergic receptors may contribute to the hemodynamic effects of etomidate.

Etomidate's remarkably benign cardiovascular and pulmonary effects are also likely the result of its selectivity for a few molecular targets. In comparison, clinically relevant concentrations of barbiturates, propofol, and volatile anesthetics modulate a broader array of $GABA_A$ receptor subtypes together with multiple other etomidate-insensitive ion channels found in both neurons and cardiovascular structures.[149]

Channels That Mediate Etomidate Injection Pain

Transient receptor potential type A1 cation channels are involved in inflammation and pain sensation. Like propofol and other general anesthetics, etomidate at high concentrations activates transient receptor potential type A1 channels, a mechanism that may underlie pain during injection.[150]

New Drugs Based on Etomidate

Selective Adrenal Steroid Inhibitors

Because of its unequaled potency as an inhibitor of cortisol and aldosterone synthesis, etomidate derivatives have been explored as selective biomarkers and inhibitors for diseases associated with excess adrenocortical activity. Positron-emitting derivatives of etomidate have been developed for localization of adrenal tumors,[151] and infusion of etomidate is gaining popularity as a short-term treatment for poorly controlled Cushing's disease.[152] Subhypnotic doses of etomidate effectively reduce the high systemic cortisol and aldosterone concentrations associated with this disease, with mild sedation as an adverse effect.[153] In addition to inhibiting steroid synthesis, etomidate inhibits proliferation of adrenal cortical cells, making it particularly useful in the treatment of metastatic adrenocortical tumors.[154] In a recent report[79] on several dozen synthetic etomidate derivatives, none demonstrated greater potency than etomidate for inhibition of cortisol synthesis by cultured adrenal cells. Several of these compounds show high potency for CYP11B binding but weak interactions with $GABA_A$ receptors, suggesting that treatment for excess cortisol or aldosterone synthesis may be achieved without adverse sedative effects.[155]

Novel Anesthetic Agents

Recent research has also aimed at modifying etomidate to improve its clinical utility as an anesthetic and sedative. Two molecular strategies have been described to maintain the favorable clinical features of etomidate while reducing the ac-

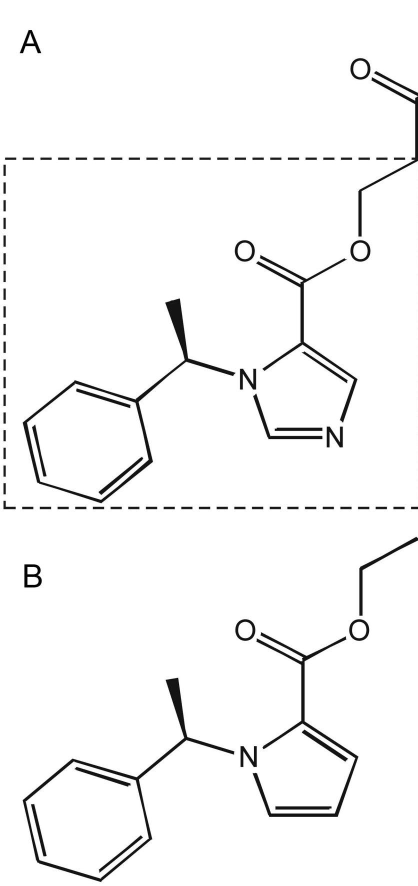

Fig. 7. Structures of MOC etomidate and carboetomidate. (*A*) Structure of MOC etomidate, a rapidly metabolized "soft analog" of etomidate. The *dashed box* outlines the parent molecule, which is depicted in Fig. 1. (*B*) Structure of carboetomidate, a molecule that retains the molecular shape of etomidate while replacing the imidazole ring with a pyrrole ring that is unable to form coordinate bonds with heme iron. (The structures were kindly provided by Douglas Raines, M.D., Department of Anesthesia, Critical Care, and Pain Medicine, Massachusetts General Hospital, Boston, Massachusetts.)

tivity that most limits its clinical use: prolonged inhibition of adrenal steroidogenesis.

Methoxycarbonyl (MOC) etomidate is a "soft" analog that contains a second ester bond distal to the existing etomidate ester linkage (fig. 7A).[156] MOC etomidate modulates $GABA_A$ receptors with a potency near that of etomidate but is rapidly (with a half-life of a few minutes) metabolized by nonspecific esterase enzymes in blood and tissue and converted to a carboxylic acid metabolite. The MOC etomidate metabolite is inactive as both an anesthetic and an inhibitor of adrenal steroid synthesis (Douglas Raines, M.D., Department of Anesthesia, Critical Care, and Pain Medicine, Massachusetts General Hospital; oral communication; April, 2010). In rats, MOC etomidate bolus administration produced anesthesia lasting only a few minutes, whereas an equipotent bolus of etomidate produced loss of righting reflexes for nearly an hour. Thirty minutes after MOC etomidate bolus administration, no adrenal suppression is found, whereas significant adrenal suppression is associated with etomidate bolus administration. MOC etomidate is in preclinical development. Its potential use includes anesthesia induction and maintenance for up to several hours. Adrenal suppression may be present during anesthesia with MOC etomidate, but adrenal function is predicted to recover rapidly after cessation of drug infusion.

Carboetomidate is an etomidate "look-alike" drug that contains a five-membered pyrrole ring instead of an imidazole (fig. 7B).[157] The loss of the free imidazole nitrogen eliminates coordination interactions with heme irons, reducing adrenal suppression potency by three orders of magnitude (IC_{50}, approximately 1 μM [*vs.* etomidate IC_{50}, 1 nM]), based on adrenal cell cortisol synthesis assays. Carboetomidate retains the ability to modulate and directly activate $GABA_A$ receptors and is a potent sedative–hypnotic with systemic effects and a duration of action similar to that of etomidate in laboratory animals.

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