

Clinical and Molecular Pharmacology of Etomidate

Stuart A. Forman, M.D., Ph.D.*

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.

* Associate Professor of Anaesthesia, Harvard Medical School, Boston, Massachusetts, and Associate Anesthetist, Department of Anesthesia, Critical Care, and Pain Medicine, Massachusetts General Hospital, Boston, Massachusetts.

Received from Massachusetts General Hospital, Boston, Massachusetts. Submitted for publication July 6, 2010. Accepted for publication September 17, 2010. Supported by grant P01GM58448 from the National Institutes of Health (Bethesda, Maryland); and the Department of Anesthesia, Critical Care, and Pain Medicine, Massachusetts General Hospital, Boston, Massachusetts. Massachusetts General Hospital has submitted patent applications for MOC etomidate, carboetomidate, and related analogs. The author and his laboratory, department, and institution could receive royalties relating to the development or sale of these drugs.

Address correspondence to Dr. Forman: Department of Anesthesia, Critical Care, and Pain Medicine, Jackson 444, Massachusetts General Hospital, 55 Fruit Street, Boston, Massachusetts 02114. saforman@partners.org. Information on purchasing reprints may be found at www.anesthesiology.org or on the masthead page at the beginning of this issue. ANESTHESIOLOGY's articles are made freely accessible to all readers, for personal use only, 6 months from the cover date of the issue.

Copyright © 2011, the American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins. Anesthesiology 2011; 114: 695–707

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 esters¹ synthesized by Janssen Pharmaceuticals (a division of Ortho-McNeil-Janssen 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/ED₅₀, approximately 12) compared with barbiturates with median lethal dose/ED₅₀ 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/ED₅₀ 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.

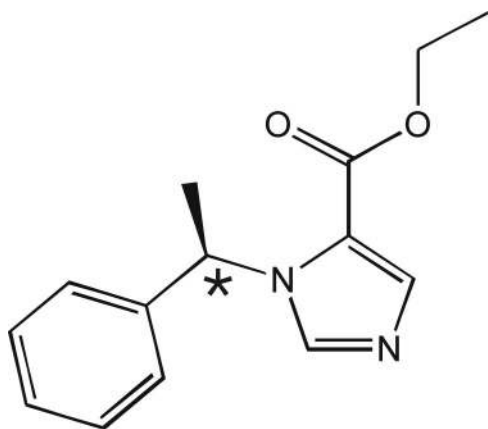


Fig. 1. Chemical structure of etomidate. Critical structural features for anesthetic activity include a single methylene group between the imidazole and phenyl group and the *R*(+) configuration at the chiral center (labeled with an asterisk).

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 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$.^{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*
<i>R</i> (+)-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.

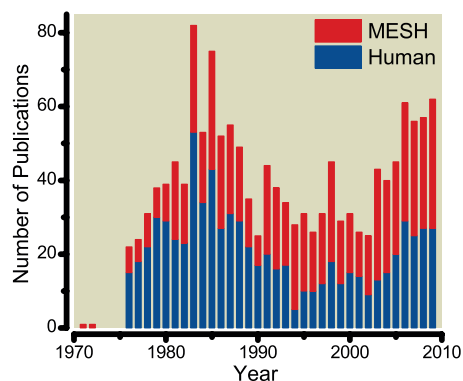


Fig. 2. Etomidate publications in PubMed. The graph displays numbers of publications within a calendar year, based on PubMed searches with *etomidate* as a Medical Subject Headings term (sum of red plus blue bars) or the subset of these publications with humans as the subjects (blue bars only). Data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

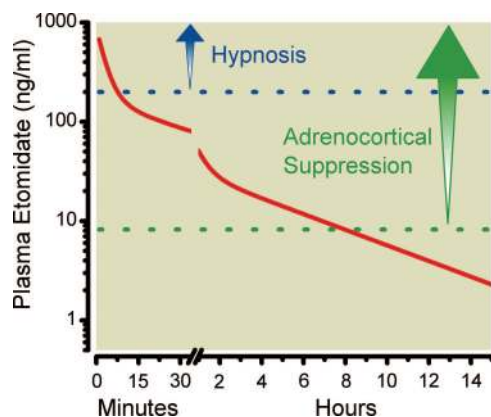


Fig. 3. Single intravenous bolus pharmacokinetics of etomidate. The etomidate plasma concentration after a single intravenous bolus (3 mg/kg) is depicted on a semilogarithmic plot with the early decline period expanded. This concentration *versus* time profile is based on pharmacokinetic parameters determined 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 · kg⁻¹ · 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 clear-

ance.^{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 induction⁵⁸ 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.

In 1983, a decade after its introduction into clinical use, Ledingham and Watt⁶⁶ 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 Finlay⁶⁸ 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 research⁷⁸ 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 μ M), whereas concentrations less than 10 ng/ml are associated with adrenal cortical suppression.⁷² The *in vitro* IC₅₀ 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 study⁸² 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}

† 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.

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 McKeown⁹¹ also found no evidence of excess mortality associated with etomidate in a retrospective study. A recent randomized controlled trial⁹² 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

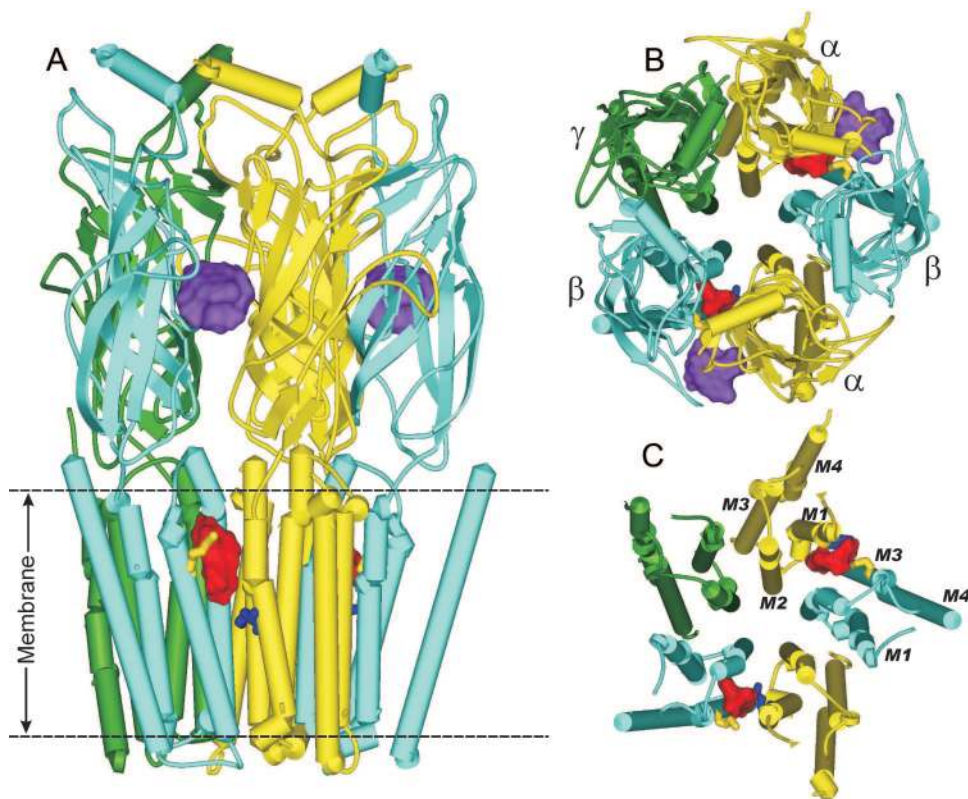


Fig. 4. Molecular structure of GABA_A receptors. A GABA_A receptor homology model, based on the structure of *Torpedo* nicotinic acetylcholine receptors, is shown in two views. The subunits are color coded: α , yellow; β , blue; γ , green. (A) The receptor is depicted in a membrane cross-sectional view, 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, α M236 (blue) and β M286 (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 α 1, β 2, and γ 2 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 syn-

aptic 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 Uchida¹¹⁵ 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 β 2 and/or β 3 subunits are modulated and activated by etomidate, whereas those containing β 1 are much less sensitive to both etomidate actions.^{113,117,120} Etomidate sensitivity is also affected by the presence of a γ subunit¹¹³ 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 α 1 β 2 γ 2L 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 μ M) to closed receptors but tightly (K_E^* , approximately 0.27 μ M) 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 β 1 *versus* β 2 subunits.¹²¹ The only amino acid in M2 that differs between β 1 and β 2 is at position 265 of the mature protein. β 265 is a serine (S) in β 1 and an asparagine (N) in β 2 and β 3. A point mutation replacing β 1S265 with N (β 1S265N) increases etomidate sensitivity, whereas replacing β 2 or β 3N265 with S (β 2/3N265S) dramatically reduces etomidate sensitivity.¹²¹ Similarly, an anesthetic-insensitive mutant *Drosophila melanogaster* (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 β 2 or β 3 subunit of mammalian GABA_A receptors also confers

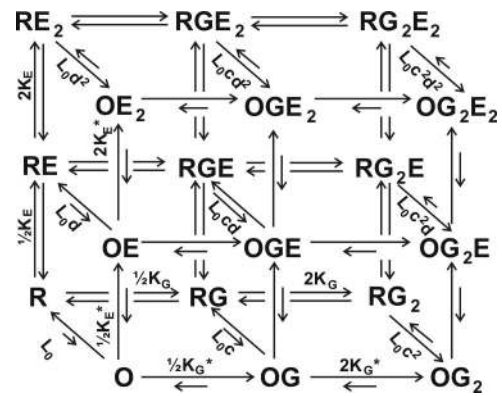


Fig. 5. Monod–Wyman–Changeux two-state equilibrium model for etomidate and GABA activation of GABA_A receptors. The scheme depicts allosteric coagonism for GABA_A receptors with two equivalent GABA (G; orthosteric agonist) sites and two equivalent etomidate (E; allosteric agonist) sites. The L_0 parameter 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 β N265 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 β 2N265S and β 2N265M mutations show little impact on basal or GABA-mediated activation and different degrees of reduced etomidate sensitivity.¹²⁵ The β 2N265M mutation totally eliminates etomidate sensitivity, whereas the β 2N265S mutation reduces etomidate-induced shifts in GABA EC₅₀ (EC₅₀ 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 β M286 mutations also influence etomidate sensitivity. The β M286W mutation eliminates etomidate modulation of receptors, whereas the homologous α A291W mutation has no effect on etomidate actions.^{123,124,126} Quantitative electrophysiologic analysis demonstrates that GABA_A receptors containing the β M286W 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 β 2N265 and β 3N265 have been incorporated into transgenic “knock-in” mice to test the role of these subunits in anesthetic actions. Jurd *et al.*¹²⁸ reported that β 3N265M 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 EC₅₀ is the GABA concentration eliciting half-maximal activation of receptors. Etomidate EC₅₀ 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 EC₅₀ 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 α5^{-/-} animals are similar to those in wild-type littermates. Similarly, δ^{-/-} 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 di-

sulfide bonds with cysteines substituted at two α subunit M1 domain loci on the same helical face as α 1M236.

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 11 β -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

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 α 2B or α 2A adrenergic receptor subtypes. This result indicates that α 2 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

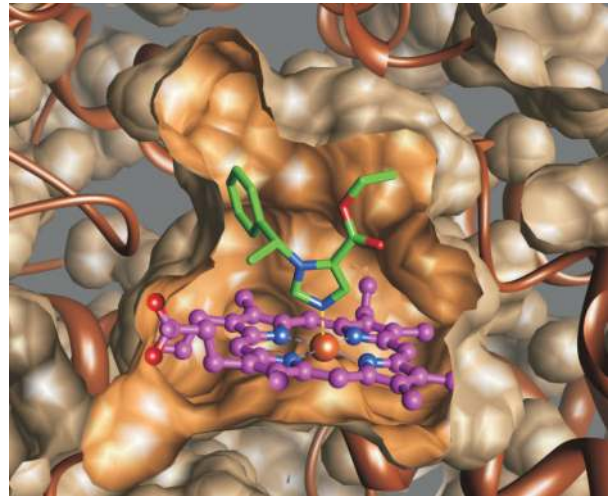


Fig. 6. Homology model for etomidate binding to CYP11B1. The binding pocket of CYP11B1 is depicted based on high-resolution crystal structures of related cytochromes.¹⁴⁷ Etomidate is bound within the binding pocket, oriented to form a strong coordinate bond between its free imidazole nitrogen and the 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.)

New Drugs Based on Etomidate

Selective Adrenal Steroid Inhibitors

Because of its unequalled 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 report⁷⁹ 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-

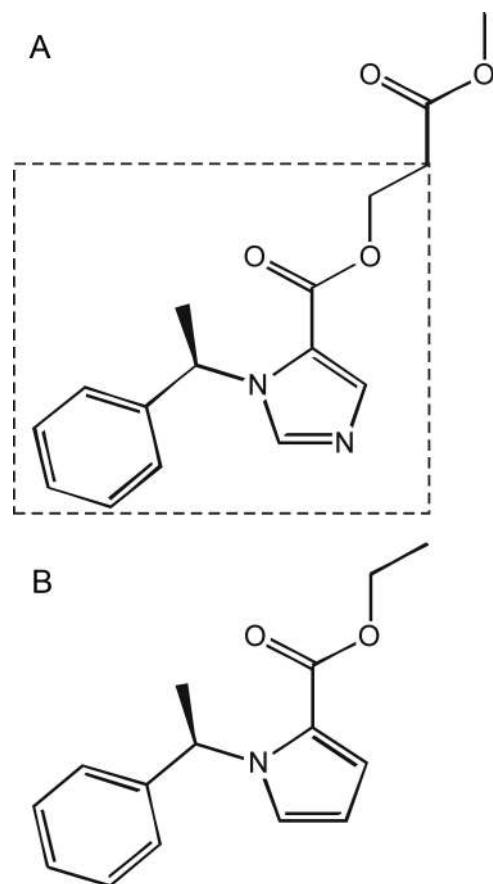


Fig. 7. Structures of MOC etomidate and carboetomidate. (A) Structure of MOC etomidate, a rapidly metabolized “soft analog” of etomidate. The *dashed box* outlines the parent molecule, which is depicted in Fig. 1. (B) Structure of carboetomidate, a molecule that retains the molecular shape of etomidate 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 pre-clinical 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 (IC₅₀, approximately 1 μM [*vs.* etomidate IC₅₀, 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.

The following individuals are thanked for contributing illustrations and valuable feedback on the manuscript: Keith W. Miller, D.Phil., Professor of Anesthesiology; Douglas Raines, M.D., Associate Professor of Anesthesiology; Joseph Cotten, M.D., Ph.D., Assistant Professor of Anesthesiology; Shunmugasundararaj Sivananthaperuma, Ph.D., Research Associate; all of the Department of Anesthesia, Critical Care, and Pain Medicine, Massachusetts General Hospital, Boston, Massachusetts; and David Chiara, M.D., Ph.D., Senior Research Associate, Department of Neurobiology, Harvard Medical School, Boston, Massachusetts.

References

- Godefroi EF, Janssen PAJ, Van der Eycken CAM, Van Heertum AHMT, Niemegeers CJ: DL-(1-arylalkyl)imidazole-5-carboxylate esters: A novel type of hypnotic agents. *J Med Chem* 1965; 56:220–3
- Tomlin SL, Jenkins A, Lieb WR, Franks NP: Stereoselective effects of etomidate optical isomers on γ -aminobutyric acid type A receptors and animals. *ANESTHESIOLOGY* 1998; 88: 708–17
- Husain SS, Ziebell MR, Ruesch D, Hong F, Arevalo E, Kosterlitz JA, Olsen RW, Forman SA, Cohen JB, Miller KW: 2-(3-Methyl-3H-diaziren-3-yl)ethyl 1-(1-phenylethyl)-1H-imidazole-5-carboxylate: A derivative of the stereoselective general anesthetic etomidate for photolabeling ligand-gated ion channels. *J Med Chem* 2003; 46:1257–65
- Janssen PA, Niemegeers CJ, Schellekens KH, Lenaerts FM: Etomidate, *R*-(+)-ethyl-1-(methyl-benzyl)imidazole-5-carboxylate (R 16659), a potent, short-acting and relatively atoxic intravenous hypnotic agent in rats. *Arzneimittelforschung* 1971; 21:1234–43
- Janssen PA, Niemegeers CJ, Marsboom RP: Etomidate, a potent non-barbiturate hypnotic. Intravenous etomidate in mice, rats, guinea-pigs, rabbits and dogs. *Arch Int Pharmacodyn Ther* 1975; 214:92–132
- Doenicke A, Wagner E, Beetz KH: Arterial blood gas analyses following administration of three short-acting i.v. hypnotics (propanidid, etomidate, methohexitone). *Anaesthetist* 1973; 22:353–6
- Morgan M, Lumley J, Whitwam JG: Etomidate, a new water-soluble non-barbiturate intravenous induction agent. *Lancet* 1975; 321:955–6
- Doenicke A, Roizen MF, Hoerneck R, Mayer M, Ostwald P, Foss J: Haemolysis after etomidate: Comparison of propylene glycol and lipid formulations. *Br J Anaesth* 1997; 79:386–8

9. Doenicke A, Roizen MF, Nebauer AE, Kugler A, Hoerneck R, Beger-Hintzen H: A comparison of two formulations for etomidate, 2-hydroxypropyl-beta-cyclodextrin (HPCD) and propylene glycol. *Anesth Analg* 1994; 79:933-9
10. McIntosh MP, Schwarting N, Rajewski RA: *In vitro* and *in vivo* evaluation of a sulfobutyl ether beta-cyclodextrin enabled etomidate formulation. *J Pharm Sci* 2004; 93:2585-94
11. Kay B: Total intravenous anesthesia with etomidate. II. Evaluation of a practical technique for children. *Acta Anaesthesiol Belg* 1977; 28:115-21
12. Scorgie B: Etomidate infusion. Its use in anaesthesia for general surgery. *Anaesthesia* 1983; 38(suppl):63-5
13. Fruergaard K, Jenstrup M, Schierbeck J, Wiberg-Jørgensen F: Total intravenous anaesthesia with propofol or etomidate. *Eur J Anaesthesiol* 1991; 8:385-91
14. Streisand JB, Jaarsma RL, Gay MA, Badger MJ, Maland L, Nordbrock E, Stanley TH: Oral transmucosal etomidate in volunteers. *ANESTHESIOLOGY* 1998; 88:89-95
15. Linton DM, Thornington RE: Etomidate as a rectal induction agent. Part II. A clinical study in children. *S Afr Med J* 1983; 64:309-10
16. Latson TW, McCarroll SM, Mirhej MA, Hyndman VA, Whitten CW, Lipton JM: Effects of three anesthetic induction techniques on heart rate variability. *J Clin Anesth* 1992; 4:265-76
17. Gelissen HP, Epema AH, Henning RH, Krijnen HJ, Hennis PJ, den Hertog A: Inotropic effects of propofol, thiopental, midazolam, etomidate, and ketamine on isolated human atrial muscle. *ANESTHESIOLOGY* 1996; 84:397-403
18. du Cailar J, Bessou D, Griffe O, Kienlen J: Hemodynamic effects of etomidate. *Ann Anesthesiol Fr* 1976; 17:1223-7
19. Criado A, Maseda J, Navarro E, Escarpa A, Avello F: Induction of anaesthesia with etomidate: Haemodynamic study of 36 patients. *Br J Anaesth* 1980; 52:803-6
20. Ebert TJ, Muzi M, Berens R, Goff D, Kampine JP: Sympathetic responses to induction of anesthesia in humans with propofol or etomidate. *ANESTHESIOLOGY* 1992; 76:725-33
21. Giese JL, Stockham RJ, Stanley TH, Pace NL, Nelissen RH: Etomidate *versus* thiopental for induction of anesthesia. *Anesth Analg* 1985; 64:871-6
22. Stockham RJ, Stanley TH, Pace NL, Gillmor S, Groen F, Hilken P: Fentanyl pretreatment modifies anaesthetic induction with etomidate. *Anaesth Intensive Care* 1988; 16:171-6
23. Bovill JG: Intravenous anesthesia for the patient with left ventricular dysfunction. *Semin Cardiothorac Vasc Anesth* 2006; 10:43-8
24. Johnson KB, Egan TD, Layman J, Kern SE, White JL, McJames SW: The influence of hemorrhagic shock on etomidate: A pharmacokinetic and pharmacodynamic analysis. *Anesth Analg* 2003; 96:1360-8
25. Johnson KB, Egan TD, Kern SE, McJames SW, Cluff ML, Pace NL: Influence of hemorrhagic shock followed by crystalloid resuscitation on propofol: A pharmacokinetic and pharmacodynamic analysis. *ANESTHESIOLOGY* 2004; 101:647-59
26. Shafer SL: Shock values. *ANESTHESIOLOGY* 2004; 101:567-8
27. Sakles JC, Laurin EG, Rantapaa AA, Panacek EA: Airway management in the emergency department: A one-year study of 610 tracheal intubations. *Ann Emerg Med* 1998; 31:325-32
28. Zuckerbraun NS, Pitetti RD, Herr SM, Roth KR, Gaines BA, King C: Use of etomidate as an induction agent for rapid sequence intubation in a pediatric emergency department. *Acad Emerg Med* 2006; 13:602-9
29. Zed PJ, Mabasa VH, Slavik RS, Abu-Laban RB: Etomidate for rapid sequence intubation in the emergency department: Is adrenal suppression a concern? *Clin J Emerg Med* 2006; 8:347-50
30. Van Hamme MJ, Ghoneim MM, Ambre JJ: Pharmacokinetics of etomidate, a new intravenous anesthetic. *ANESTHESIOLOGY* 1978; 49:274-7
31. Atiba JO, Horai Y, White PF, Trevor AJ, Blaschke TF, Sung ML: Effect of etomidate on hepatic drug metabolism in humans. *ANESTHESIOLOGY* 1988; 68:920-4
32. Cold GE, Eskesen V, Eriksen H, Amtoft O, Madsen JB: CBF and CMRO2 during continuous etomidate infusion supplemented with N2O and fentanyl in patients with supratentorial cerebral tumour. A dose-response study. *Acta Anaesthesiol Scand* 1985; 29:490-4
33. Van Aken J, Rolly G: Influence of etomidate, a new short acting anesthetic agent, on cerebral blood flow in man. *Acta Anaesthesiol Belg* 1976; 27(suppl):175-80
34. Batjer HH: Cerebral protective effects of etomidate: Experimental and clinical aspects. *Cerebrovasc Brain Metab Rev* 1993; 5:17-32
35. Ghoneim MM, Yamada T: Etomidate: A clinical and electroencephalographic comparison with thiopental. *Anesth Analg* 1977; 56:479-85
36. Lallemand MA, Lentschener C, Mazoit JX, Bonnichon P, Manceau I, Ozier Y: Bispectral index changes following etomidate induction of general anaesthesia and orotracheal intubation. *Br J Anaesth* 2003; 91:341-6
37. Kaneda K, Yamashita S, Woo S, Han TH: Population pharmacokinetics pharmacodynamics of brief etomidate infusion in healthy volunteers [published online ahead of print May 24, 2010]. *J Clin Pharmacol*, doi: 10.1177/0091270010369242
38. Thornton C, Heneghan CP, Navaratnarajah M, Bateman PE, Jones JG: Effect of etomidate on the auditory evoked response in man. *Br J Anaesth* 1985; 57:554-61
39. Ding Z, White PF: Anesthesia for electroconvulsive therapy. *Anesth Analg* 2002; 94:1351-64
40. Sloan TB, Ronai AK, Toleikis JR, Koht A: Improvement of intraoperative somatosensory evoked potentials by etomidate. *Anesth Analg* 1988; 67:582-5
41. Taniguchi M, Nadstawek J, Langenbach U, Bremer F, Schramm J: Effects of four intravenous anesthetic agents on motor evoked potentials elicited by magnetic transcranial stimulation. *Neurosurgery* 1993; 33:407-15
42. Carlos R, Calvo R, Erill S: Plasma protein binding of etomidate in patients with renal failure or hepatic cirrhosis. *Clin Pharmacokinet* 1979; 4:144-8
43. Giese JL, Stanley TH: Etomidate: A new intravenous anesthetic induction agent. *Pharmacotherapy* 1983; 3:251-8
44. Heykants JJP, Brugmans J, Doenicke A: On the pharmacokinetics of etomidate (R26490) in human volunteers: Plasma levels, metabolism, and excretion. (R26490/1 Janssen Research Product Information Service), Clinical Research Report 1975
45. Arden JR, Holley FO, Stanski DR: Increased sensitivity to etomidate in the elderly: Initial distribution *versus* altered brain response. *ANESTHESIOLOGY* 1986; 65:19-27
46. Carlos R, Calvo R, Erill S: Plasma protein binding of etomidate in different age groups and in patients with chronic respiratory insufficiency. *Int J Clin Pharmacol Ther Toxicol* 1981; 19:171-4
47. Sear J: Total intravenous anesthesia, *Anesthesiology*, 1st edition. Edited by Longnecker DE, Brown DL, Newman MF, Zapol WM. New York, McGraw Hill Medical, 2008, pp 897-917
48. Kay B: Total intravenous anesthesia with etomidate. I. A trial in children. *Acta Anaesthesiol Belg* 1977; 28:107-13
49. van de Walle J, Demeyere R, Vanacker B, Vermaut G, Vandermeresch E: Total I.V. anesthesia using a continuous etomidate infusion. *Acta Anaesthesiol Belg* 1979; 30(suppl):117-22
50. van Oss GE, Rachmat Y, Booij LH, Crul JF: Continuous infusion of etomidate as a method for outpatient anesthesia. *Acta Anaesthesiol Belg* 1980; 31:39-43

51. Edbrooke DL, Newby DM, Mather SJ, Dixon AM, Hebron BS: Safer sedation for ventilated patients. A new application for etomidate. *Anaesthesia* 1982; 37:765-71
52. Bird TM, Edbrooke DL, Newby DM, Hebron BS: Intravenous sedation for the intubated and spontaneously breathing patient in the intensive care unit. *Acta Anaesthesiol Scand* 1984; 28:640-3
53. Kay B: Some experience of the use of etomidate in children. *Acta Anaesthesiol Belg* 1976; 27(suppl):86-92
54. Kay B, Rolly G: Total intravenous anesthesia with etomidate. III. Some observations in adults. *Acta Anaesthesiol Belg* 1977; 28:157-64
55. Yelavich PM, Holmes CM: Etomidate: A foreshortened clinical trial. *Anaesth Intensive Care* 1980; 8:479-83
56. Zacharias M, Clarke RS, Dundee JW, Johnston SB: Evaluation of three preparations of etomidate. *Br J Anaesth* 1978; 50:925-9
57. Nyman Y, Von Hofsten K, Palm C, Eksborg S, Lönnqvist PA: Etomidate-lipuro is associated with considerably less injection pain in children compared with propofol with added lidocaine. *Br J Anaesth* 2006; 97:536-9
58. Doenicke AW, Roizen MF, Kugler J, Kroll H, Foss J, Ostwald P: Reducing myoclonus after etomidate. *ANESTHESIOLOGY* 1999; 90:113-9
59. Hwang JY, Kim JH, Oh AY, Do SH, Jeon YT, Han SH: A comparison of midazolam with remifentanyl for the prevention of myoclonic movements following etomidate injection. *J Int Med Res* 2008; 36:17-22
60. Mizrak A, Koruk S, Bilgi M, Kocamer B, Erkutlu I, Ganidagli S, Oner U: Pretreatment with dexmedetomidine or thiopental decreases myoclonus after etomidate: A randomized, double-blind controlled trial. *J Surg Res* 2010; 159:e11-6
61. Zacharias M, Dundee JW, Clarke RS, Hegarty JE: Effect of preanaesthetic medication on etomidate. *Br J Anaesth* 1979; 51:127-33
62. Helmers JH, Adam AA, Giezen J: Pain and myoclonus during induction with etomidate. A double-blind, controlled evaluation of the influence of droperidol and fentanyl. *Acta Anaesthesiol Belg* 1981; 32:141-7
63. Ulsamer B, Doenicke A, Laschat M: Propofol in comparison with etomidate for the induction of anesthesia. *Anaesthesist* 1986; 35:535-42
64. Mayer M, Doenicke A, Nebauer AE, Hepting L: Propofol and etomidate-lipuro for induction of general anesthesia. Hemodynamics, vascular compatibility, subjective findings and postoperative nausea. *Anaesthesist* 1996; 45:1082-4
65. St Pierre M, Dunkel M, Rutherford A, Hering W: Does etomidate increase postoperative nausea? A double-blind controlled comparison of etomidate in lipid emulsion with propofol for balanced anaesthesia. *Eur J Anaesthesiol* 2000; 17:634-41
66. Ledingham IM, Watt I: Influence of sedation on mortality in critically ill multiple trauma patients. *Lancet* 1983; 321:1270
67. Watt I, Ledingham IM: Mortality amongst multiple trauma patients admitted to an intensive therapy unit. *Anaesthesia* 1984; 39:973-81
68. McKee JI, Finlay WE: Cortisol replacement in severely stressed patients. *Lancet* 1983; 321:484
69. Preziosi P, Vacca M: Etomidate and corticotrophic axis. *Arch Int Pharmacodyn Ther* 1982; 256:308-10
70. Wagner RL, White PF, Kan PB, Rosenthal MH, Feldman D: Inhibition of adrenal steroidogenesis by the anesthetic etomidate. *N Engl J Med* 1984; 310:1415-21
71. Wagner RL, White PF: Etomidate inhibits adrenocortical function in surgical patients. *ANESTHESIOLOGY* 1984; 61:647-51
72. Fragen RJ, Shanks CA, Molteni A, Avram MJ: Effects of etomidate on hormonal responses to surgical stress. *ANESTHESIOLOGY* 1984; 61:652-6
73. Allolio B, Stuttmann R, Leonhard U, Fischer H, Winkelmann W: Adrenocortical suppression by a single induction dose of etomidate. *Klin Wochenschr* 1984; 62:1014-7
74. Wanschler M, Tønnesen E, Hüttel M, Larsen K: Etomidate infusion and adrenocortical function. A study in elective surgery. *Acta Anaesthesiol Scand* 1985; 29:483-5
75. Editorial: Etomidate. *Lancet* 1983; 322:24-5
76. Longnecker DE: Stress free: To be or not to be? *ANESTHESIOLOGY* 1984; 61:643-4
77. Owen H, Spence AA: Etomidate. *Br J Anaesth* 1984; 56:555-7
78. Diago MC, Amado JA, Otero M, Lopez-Cordovilla JJ: Adrenal action of a subanaesthetic dose of etomidate. *Anaesthesia* 1988; 43:644-5
79. Zolle IM, Berger ML, Hammerschmidt F, Hahner S, Schirbel A, Peric-Simov B: New selective inhibitors of steroid 11beta-hydroxylation in the adrenal cortex. Synthesis and structure-activity relationship of potent etomidate analogues. *J Med Chem* 2008; 51:2244-53
80. Annane D, Sébille V, Charpentier C, Bollaert PE, François B, Korach JM, Capellier G, Cohen Y, Azoulay E, Troché G, Chaumet-Riffaud P, Bellissant E: Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA* 2002; 288:862-71
81. Annane D, Sebille V: Corticosteroids for patients with septic shock. *JAMA* 2003; 289:43-4
82. Sprung CL, Annane D, Keh D, Moreno R, Singer M, Freivogel K, Weiss YG, Benbenishty J, Kalenka A, Forst H, Laterre PF, Reinhart K, Cuthbertson BH, Payen D, Briegel J, CORTICUS Study Group: Hydrocortisone therapy for patients with septic shock. *N Engl J Med* 2008; 358:111-24
83. Mohammad Z, Afessa B, Finkielman JD: The incidence of relative adrenal insufficiency in patients with septic shock after the administration of etomidate. *Crit Care* 2006; 10:R105
84. Lipiner-Friedman D, Sprung CL, Laterre PF, Weiss Y, Goodman SV, Vogeser M, Briegel J, Keh D, Singer M, Moreno R, Bellissant E, Annane D: Adrenal function in sepsis: The retrospective Corticus cohort study. *Crit Care Med* 2007; 35:1012-8
85. Cuthbertson BH, Sprung CL, Annane D, Chevret S, Garfield M, Goodman S, Laterre PF, Vincent JL, Freivogel K, Reinhart K, Singer M, Payen D, Weiss YG: The effects of etomidate on adrenal responsiveness and mortality in patients with septic shock. *Intensive Care Med* 2009; 35:1868-76
86. Vinclair M, Broux C, Faure P, Brun J, Genty C, Jacquot C, Chabre O, Payen JF: Duration of adrenal inhibition following a single dose of etomidate in critically ill patients. *Intensive Care Med* 2008; 34:714-9
87. Absalom A, Pledger D, Kong A: Adrenocortical function in critically ill patients 24 h after a single dose of etomidate. *Anaesthesia* 1999; 54:861-7
88. den Brinker M, Hokken-Koelega AC, Hazelzet JA, de Jong FH, Hop WC, Joosten KF: One single dose of etomidate negatively influences adrenocortical performance for at least 24 h in children with meningococcal sepsis. *Intensive Care Med* 2008; 34:163-8
89. Hildreth AN, Mejia VA, Maxwell RA, Smith PW, Dart BW, Barker DE: Adrenal suppression following a single dose of etomidate for rapid sequence induction: A prospective randomized study. *J Trauma* 2008; 65:573-9
90. Tekwani KL, Watts HF, Rzechula KH, Sweis RT, Kulstad EB: A prospective observational study of the effect of etomidate on septic patient mortality and length of stay. *Acad Emerg Med* 2009; 16:11-4
91. Ray DC, McKeown DW: Effect of induction agent on vaso-

- pressor and steroid use, and outcome in patients with septic shock. *Crit Care* 2007; 11:R56
92. Jabre P, Combes X, Lapostolle F, Dhauadi M, Ricard-Hibon A, Vivien B, Bertrand L, Beltrami A, Gamand P, Albizzati S, Perdrizet D, Leblai G, Chollet-Xemard C, Maxime V, Brun-Buisson C, Lefrant JY, Bollaert PE, Megarbane B, Ricard JD, Anguel N, Vicaut E, Adnet F, KETASED Collaborative Study Group: Etomidate *versus* ketamine for rapid sequence intubation in acutely ill patients: A multicentre randomised controlled trial. *Lancet* 2009; 374:293-300
 93. Jackson WL Jr: Should we use etomidate as an induction agent for endotracheal intubation in patients with septic shock? A critical appraisal. *Chest* 2005; 127:1031-8
 94. Walls RM, Murphy MF: Clinical controversies: Etomidate as an induction agent for endotracheal intubation in patients with sepsis: Continue to use etomidate for intubation of patients with septic shock. *Ann Emerg Med* 2008; 52:13-4
 95. Krasowski MD, Harrison NL: General anaesthetic actions on ligand-gated ion channels. *Cell Mol Life Sci* 1999; 55:1278-303
 96. Rudolph U, Antkowiak B: Molecular and neuronal substrates for general anaesthetics. *Nat Rev Neurosci* 2004; 5:709-20
 97. Evans RH, Hill RG: GABA-mimetic action of etomidate. *Experientia* 1978; 34:1325-7
 98. Carlson BX, Hales TG, Olsen RW: GABA-A receptors and anesthesia. *Anesthesia Biologic Foundations*. Edited by Yaksh TL, Lynch C, Zapol WM, Maze M, Biebuyck JF, Saidman LJ. Philadelphia, Lippincott-Raven, 1998, pp 259-76
 99. Brejc K, van Dijk WJ, Klaassen RV, Schuurmans M, van Der Oost J, Smit AB, Sixma TK: Crystal structure of an ACh-binding protein reveals the ligand-binding domain of nicotinic receptors. *Nature* 2001; 411:269-76
 100. Unwin N: Refined structure of the nicotinic acetylcholine receptor at 4Å resolution. *J Mol Biol* 2005; 346:967-89
 101. Bocquet N, Nury H, Baaden M, Le Poupon C, Changeux JP, Delarue M, Corringer PJ: X-ray structure of a pentameric ligand-gated ion channel in an apparently open conformation. *Nature* 2009; 457:111-4
 102. Hilf RJ, Dutzler R: Structure of a potentially open state of a proton-activated pentameric ligand-gated ion channel. *Nature* 2009; 457:115-8
 103. Hilf RJ, Dutzler R: X-ray structure of a prokaryotic pentameric ligand-gated ion channel. *Nature* 2008; 452:375-9
 104. Olsen RW, Sieghart W: GABA(A) receptors: Subtypes provide diversity of function and pharmacology. *Neuropharmacology* 2008; 56:141-8
 105. Baumann SW, Baur R, Sigel E: Subunit arrangement of gamma-aminobutyric acid type A receptors. *J Biol Chem* 2001; 276:36275-80
 106. McKernan RM, Whiting PJ: Which GABAA-receptor subtypes really occur in the brain? *Trends Neurosci* 1996; 19:139-43
 107. Segal M, Barker JL: Rat hippocampal neurons in culture: Voltage-clamp analysis of inhibitory synaptic connections. *J Neurophysiol* 1984; 52:469-87
 108. Vierling-Claassen D, Siekmeier P, Stufflebeam S, Kopell N: Modeling GABA alterations in schizophrenia: A link between impaired inhibition and altered gamma and beta range auditory entrainment. *J Neurophysiol* 2008; 99:2656-71
 109. Whittington MA, Traub RD, Kopell N, Ermentrout B, Buhl EH: Inhibition-based rhythms: Experimental and mathematical observations on network dynamics. *Int J Psychophysiol* 2000; 38:315-36
 110. Banks MI, Pearce RA: Kinetic differences between synaptic and extrasynaptic GABA(A) receptors in CA1 pyramidal cells. *J Neurosci* 2000; 20:937-48
 111. Herd MB, Belelli D, Lambert JJ: Neurosteroid modulation of synaptic and extrasynaptic GABA(A) receptors. *Pharmacol Ther* 2007; 116:20-34
 112. Sem'yanov AV: Diffusional extrasynaptic neurotransmission *via* glutamate and GABA. *Neurosci Behav Physiol* 2005; 35:253-66
 113. Uchida I, Kamatchi G, Burt D, Yang J: Etomidate potentiation of GABAA receptor gated current depends on the subunit composition. *Neurosci Lett* 1995; 185:203-6
 114. Rüschi D, Zhong H, Forman SA: Gating allosterism at a single class of etomidate sites on alpha1beta2gamma2L GABA-A receptors accounts for both direct activation and agonist modulation. *J Biol Chem* 2004; 279:20982-92
 115. Yang J, Uchida I: Mechanisms of etomidate potentiation of GABAA receptor-gated currents in cultured postnatal hippocampal neurons. *Neuroscience* 1996; 73:69-78
 116. Zhong H, Rüschi D, Forman SA: Photo-activated azi-etomidate, a general anesthetic photolabel, irreversibly enhances gating and desensitization of γ -aminobutyric acid type A receptors. *ANESTHESIOLOGY* 2008; 108:103-12
 117. Hill-Venning C, Belelli D, Peters JA, Lambert JJ: Subunit-dependent interaction of the general anaesthetic etomidate with the gamma-aminobutyric acid type A receptor. *Br J Pharmacol* 1997; 120:749-56
 118. Ashton D, Wauquier A: Modulation of a GABA-ergic inhibitory circuit in the *in vitro* hippocampus by etomidate isomers. *Anesth Analg* 1985; 64:975-80
 119. Belelli D, Muntoni AL, Merrywest SD, Gentet IJ, Casula A, Callachan H, Madau P, Gemmill DK, Hamilton NM, Lambert JJ, Sillar KT, Peters JA: The *in vitro* and *in vivo* enantioselectivity of etomidate implicates the GABA_A receptor in general anaesthesia. *Neuropharmacology* 2003; 45:57-71
 120. Sanna E, Murgia A, Casula A, Biggio G: Differential subunit dependence of the actions of the general anesthetics alphaxalone and etomidate at gamma-aminobutyric acid type A receptors expressed in *Xenopus laevis* oocytes. *Mol Pharmacol* 1997; 51:484-90
 121. Belelli D, Lambert JJ, Peters JA, Wafford K, Whiting PJ: The interaction of the general anesthetic etomidate with the gamma-aminobutyric acid type A receptor is influenced by a single amino acid. *Proc Natl Acad Sci USA* 1997; 94:11031-6
 122. McGurk KA, Pistis M, Belelli D, Hope AG, Lambert JJ: The effect of a transmembrane amino acid on etomidate sensitivity of an invertebrate GABA receptor. *Br J Pharmacol* 1998; 124:13-20
 123. Siegwart R, Jurd R, Rudolph U: Molecular determinants for the action of general anesthetics at recombinant alpha(2)beta(3)gamma(2)gamma-aminobutyric acid(A) receptors. *J Neurochem* 2002; 80:140-8
 124. Siegwart R, Krahenbuhl K, Lambert S, Rudolph U: Mutational analysis of molecular requirements for the actions of general anaesthetics at the gamma-aminobutyric acidA receptor subtype, alpha1beta2gamma2. *BMC Pharmacol* 2003; 3:13
 125. Desai R, Ruesch D, Forman SA: γ -Aminobutyric acid type A receptor mutations at β 2N265 alter etomidate efficacy while preserving basal and agonist-dependent activity. *ANESTHESIOLOGY* 2009; 111:774-84
 126. Krasowski MD, Koltchine VV, Rick CE, Ye Q, Finn SE, Harrison NL: Propofol and other intravenous anesthetics have sites of action on the gamma-aminobutyric acid type A receptor distinct from that for isoflurane. *Mol Pharmacol* 1998; 53:530-8
 127. Stewart D, Desai R, Cheng Q, Liu A, Forman SA: Tryptophan mutations at azi-etomidate photo-incorporation sites on alpha1 or beta2 subunits enhance GABAA receptor gating and reduce etomidate modulation. *Mol Pharmacol* 2008; 74:1687-95
 128. Jurd R, Arras M, Lambert S, Drexler B, Siegwart R, Crestani F, Zaugg M, Vogt KE, Ledermann B, Antkowiak B, Rudolph

- U: General anesthetic actions *in vivo* strongly attenuated by a point mutation in the GABA(A) receptor beta3 subunit. *FASEB J* 2003; 17:250-2
129. Reynolds DS, Rosahl TW, Cirone J, O'Meara GF, Haythornthwaite A, Newman RJ, Myers J, Sur C, Howell O, Rutter AR, Atack J, Macaulay AJ, Hadingham KL, Hutson PH, Belelli D, Lambert JJ, Dawson GR, McKernan R, Whiting PJ, Wafford KA: Sedation and anesthesia mediated by distinct GABA(A) receptor isoforms. *J Neurosci* 2003; 23:8608-17
 130. Cirone J, Rosahl TW, Reynolds DS, Newman RJ, O'Meara GF, Hutson PH, Wafford KA: γ -Aminobutyric acid type A receptor β 2 subunit mediates the hypothermic effect of etomidate in mice. *ANESTHESIOLOGY* 2004; 100:1438-45
 131. Herd MB, Haythornthwaite AR, Rosahl TW, Wafford KA, Homanics GE, Lambert JJ, Belelli D: The expression of GABAA beta subunit isoforms in synaptic and extrasynaptic receptor populations of mouse dentate gyrus granule cells. *J Physiol* 2008; 586:989-1004
 132. Cheng VY, Martin LJ, Elliott EM, Kim JH, Mount HT, Taverna FA, Roder JC, Macdonald JF, Bhambri A, Collinson N, Wafford KA, Orser BA: Alpha5GABAA receptors mediate the amnestic but not sedative-hypnotic effects of the general anesthetic etomidate. *J Neurosci* 2006; 26:3713-20
 133. Mihalek RM, Banerjee PK, Korpi ER, Quinlan JJ, Firestone LL, Mi ZP, Lagenaur C, Tretter V, Sieghart W, Anagnostaras SG, Sage JR, Fanselow MS, Guidotti A, Spigelman I, Li Z, DeLorey TM, Olsen RW, Homanics GE: Attenuated sensitivity to neuroactive steroids in gamma-aminobutyrate type A receptor delta subunit knockout mice. *Proc Natl Acad Sci U S A* 1999; 96:12905-10
 134. Bright DP, Adham SD, Lemaire LC, Benavides R, Gruss M, Taylor GW, Smith EH, Franks NP: Identification of anesthetic binding sites on human serum albumin using a novel etomidate photolabel. *J Biol Chem* 2007; 282:12038-47
 135. Liao M, Sonner JM, Husain SS, Miller KW, Jurd R, Rudolph U, Eger EI 2nd: *R* (+) etomidate and the photoactivable *R* (+) azietomidate have comparable anesthetic activity in wild-type mice and comparably decreased activity in mice with a N265M point mutation in the γ -aminobutyric acid receptor beta3 subunit. *Anesth Analg* 2005; 101:131-5
 136. Li GD, Chiara DC, Sawyer GW, Husain SS, Olsen RW, Cohen JB: Identification of a GABAA receptor anesthetic binding site at subunit interfaces by photolabeling with an etomidate analog. *J Neurosci* 2006; 26:11599-605
 137. Bali M, Jansen M, Akabas MH: GABA-induced intersubunit conformational movement in the GABAA receptor alpha1M1-beta2M3 transmembrane subunit interface: Experimental basis for homology modeling of an intravenous anesthetic binding site. *J Neurosci* 2009; 29:3083-92
 138. Jenkins A, Greenblatt EP, Faulkner HJ, Bertaccini E, Light A, Lin A, Andreasen A, Viner A, Trudell JR, Harrison NL: Evidence for a common binding cavity for three general anesthetics within the GABAA receptor. *J Neurosci* 2001; 21:RC136
 139. Dörr HG, Kuhnle U, Holthausen H, Bidlingmaier F, Knorr D: Etomidate: A selective adrenocortical 11 beta-hydroxylase inhibitor. *Klin Wochenschr* 1984; 62:1011-3
 140. Varga I, Rác K, Kiss R, Fütö L, Tóth M, Sergev O, Gláz E: Direct inhibitory effect of etomidate on corticosteroid secretion in human pathologic adrenocortical cells. *Steroids* 1993; 58:64-8
 141. Mornet E, Dupont J, Vitek A, White PC: Characterization of two genes encoding human steroid 11 beta-hydroxylase (P-450(11) beta). *J Biol Chem* 1989; 264:20961-7
 142. Ullerås E, Ohlsson A, Oskarsson A: Secretion of cortisol and aldosterone as a vulnerable target for adrenal endocrine disruption: Screening of 30 selected chemicals in the human H295R cell model. *J Appl Toxicol* 2008; 28:1045-53
 143. Poulos TL, Howard AJ: Crystal structures of metyrapone- and phenylimidazole-inhibited complexes of cytochrome P-450cam. *Biochemistry* 1987; 26:8165-74
 144. Gay SC, Sun L, Maekawa K, Halpert JR, Stout CD: Crystal structures of cytochrome P450 2B4 in complex with the inhibitor 1-biphenyl-4-methyl-1H-imidazole: Ligand-induced structural response through alpha-helical repositioning. *Biochemistry* 2009; 48:4762-71
 145. Ouellet H, Podust LM, de Montellano PR: Mycobacterium tuberculosis CYP130: Crystal structure, biophysical characterization, and interactions with antifungal azole drugs. *J Biol Chem* 2008; 283:5069-80
 146. Zöllner A, Kagawa N, Waterman MR, Nonaka Y, Takio K, Shiro Y, Hannemann F, Bernhardt R: Purification and functional characterization of human 11beta hydroxylase expressed in *Escherichia coli*. *FEBS J* 2008; 275:799-810
 147. Roumen L, Sanders MP, Pieterse K, Hilbers PA, Plate R, Custers E, de Gooyer M, Smits JF, Beugels I, Emmen J, Ottenheim HC, Leysen D, Hermans JJ: Construction of 3D models of the CYP11B family as a tool to predict ligand binding characteristics. *J Comput Aided Mol Des* 2007; 21:455-71
 148. Paris A, Philipp M, Tonner PH, Steinfath M, Lohse M, Scholz J, Hein L: Activation of α 2B-adrenoceptors mediates the cardiovascular effects of etomidate. *ANESTHESIOLOGY* 2003; 99:889-95
 149. Alkire MT, Hudetz AG, Tononi G: Consciousness and anesthesia. *Science* 2008; 322:876-80
 150. Matta JA, Cornett PM, Miyares RL, Abe K, Sahibzada N, Ahern GP: General anesthetics activate a nociceptive ion channel to enhance pain and inflammation. *Proc Natl Acad Sci USA* 2008; 105:8784-9
 151. Hahner S, Stuermer A, Kreissl M, Reiners C, Fassnacht M, Haenschel H, Beuschlein F, Zink M, Lang K, Alolio B, Schirbel A: [123 I]iodometomidate for molecular imaging of adrenocortical cytochrome P450 family 11B enzymes. *J Clin Endocrinol Metab* 2008; 93:2358-65
 152. Igaz P, Tömböl Z, Szabó PM, Likó I, Rác K: Steroid biosynthesis inhibitors in the therapy of hypercortisolism: Theory and practice. *Curr Med Chem* 2008; 15:2734-47
 153. Schulte HM, Benker G, Reinwein D, Sippell WG, Alolio B: Infusion of low dose etomidate: Correction of hypercortisolemia in patients with Cushing's syndrome and dose-response relationship in normal subjects. *J Clin Endocrinol Metab* 1990; 70:1426-30
 154. Fassnacht M, Hahner S, Beuschlein F, Klink A, Reincke M, Alolio B: New mechanisms of adrenostatic compounds in a human adrenocortical cancer cell line. *Eur J Clin Invest* 2000; 30(suppl 3):76-82
 155. Atucha E, Hammerschmidt F, Zolle I, Sieghart W, Berger ML: Structure-activity relationship of etomidate derivatives at the GABA(A) receptor: Comparison with binding to 11beta-hydroxylase. *Bioorg Med Chem Lett* 2009; 19:4284-7
 156. Cotten JF, Husain SS, Forman SA, Miller KW, Kelly EW, Nguyen HH, Raines DE: Methoxycarbonyl-etomidate: A novel rapidly metabolized and ultra-short-acting etomidate analogue that does not produce prolonged adrenocortical suppression. *ANESTHESIOLOGY* 2009; 111:240-9
 157. Cotten JF, Forman SA, Laha JK, Cuny GD, Husain SS, Miller KW, Nguyen HH, Kelly EW, Stewart D, Liu A, Raines DE: Carboetomidate: A pyrrole analog of etomidate designed not to suppress adrenocortical function. *ANESTHESIOLOGY* 2010; 112:637-44
 158. Glen JB: Animal studies of the anaesthetic activity of ICI 35 868. *Br J Anaesth* 1980; 52:731-42
 159. Marietta MP, Way WL, Castagnoli N Jr, Trevor AJ: On the pharmacology of the ketamine enantiomorphs in the rat. *J Pharmacol Exp Ther* 1977; 202:157-65
 160. Christensen HD, Lee IS: Anesthetic potency and acute toxicity of optically active disubstituted barbituric acids. *Toxicol Appl Pharmacol* 1973; 26:495-503