

Etomidate derivatives: Novel pharmaceutical agents in anesthesia

Raymond J. Malapero1,2, Michael P. Zaccagnino1,2, Ethan Y. Brovman1,2, Alan David Kaye3,4, Richard D. Urman1,2

1Department of Anesthesiology, Perioperative and Pain Medicine, Harvard Medical School, 2Department of Anesthesiology, Perioperative and Pain Medicine, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA 02115, Departments of 3Anesthesiology, 4Pharmacology, Louisiana State University Health Science Center, New Orleans, LA 70112, USA

Abstract

Etomidate is an imidazole derivative that possesses important sedative properties employed in anesthesia practice, however, etomidate has a number of well-known side effects which limit its use in certain subpopulations and over long periods of time, mostly related to dose-dependent adrenal suppression. This review focuses on novel etomidate derivatives with an emphasis on pharmacological properties which afford improved safety profile and potentially desirable clinical effects. The pharmacology and clinical investigation of some of these etomidate derivatives, e.g. cyclopropyl-methoxycarbonyl, carboetomidate metomidate, methoxycarbonyl-etomidate, cyclopropyl-methoxycarbonyl metomidate (CPMM), and dimethyl-methoxycarbonyl metomidate, are discussed in detail. The increased potency and decreased metabolite build-up of CPMM potentially makes it a very favorable drug, particularly in the setting of prolonged infusions. Further, when compared with etomidate, CPMM produces lower plasma cytokine concentration and improved survival in lipopolysaccharide inflammatory sepsis models.

Key words: Adrenal suppression, carboetomidate metomidate, cyclopropyl-methoxycarbonyl, cyclopropyl-methoxycarbonyl metomidate, dimethyl-methoxycarbonyl metomidate, etomidate, imidazole, methoxycarbonyl-etomidate

Introduction

Etomidate was first developed in 1964 by Janssen Pharmaceuticals. Its first clinical use was in 1972, and numerous publications on etomidate ensued until 1983, when numerous reports of adrenal suppression were described. Renewal of interest in etomidate came with increased use by emergency medicine physicians and anesthesiologists for emergent intubations in unstable patients. Etomidate is a short-acting agent that is known for its cardiovascular stability with induction, and is frequently cited for its role in sedation and anesthetic induction. However, its adrenal suppression is often described as potentially dangerous to patients, especially in the critically-ill populations for whom etomidate-based inductions are most commonly used.[1-5]

Pharmacological Properties

Etomidate is an imidazole derivative that (in particular, the more clinically active R+ isomer) binds the gamma aminobutyric acid A (GABA_A) receptor, resulting in depression of the reticular activating system. Its rapid onset is secondary to its lipid solubility and is largely nonionized at physiologic pH. Etomidate leaves myocyte contractility and cardiac output largely unchanged, and causes only a

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modest decrease in arterial blood pressure (often described as within 10% of baseline with standard induction doses). Ventilation is minimally affected with etomidate, and cerebral metabolic rate, cerebral blood flow, and intracranial pressure are decreased. These characteristics of etomidate make it an ideal option for brief, deep sedation, and for induction of general anesthesia. Negative properties of etomidate include lack of analgesic properties, provocation of postoperative nausea, reduced seizure thresholds, propylene glycol-mediated pain on intravenous (IV) injection, and extrapyramidal disinhibitory effects, which explain myoclonus often seen after administration. Most significantly, etomidate causes adrenocortical suppression by inhibition of 11 beta-hydroxylase, which can negatively impact outcomes of critically-ill patients. In the case of adrenal suppression, the adrenal glands do not produce enough of the steroid hormones, namely cortisol. Sequelae of adrenal insufficiency include low cortisol levels, hyponatremia, hypoglycemia, hyperkalemia, hypercalcemia, altered mental status, hypotension, and metabolic acidosis. Etomidate is distributed as a 2 mg/ml solution, which has a pKa of 4.2 and is highly lipid soluble at a physiologic pH, requiring it to be dissolved in propylene glycol. By-products are largely secreted in the urine following hydrolysis.

**Novel Etomidate Derivatives**

**Carboetomidate**

To mitigate adrenal suppressive effects of etomidate, novel derivatives have been developed from the base structure of the etomidate molecule. The nitrogen of etomidate imidazole ring bonds with the 11 beta-hydroxylase enzyme, and by substituting this nitrogen with a methylene group, carboetomidate is formed. This substitution is significant because it allows a 2000-fold lower adrenocortical inhibitory level in vitro, thus possessing etomidate-mediated hypnotic effects with a significantly reduced risk of adrenal suppression. With the issue of adrenal suppression eliminated from etomidate, further benefits can be sought. For instance, maintaining immunomodulatory activity with carboetomidate, even after repeat bolus dosing in sepsis, could provide great benefit in the critical care setting. Prior to this discovery, etomidate in the setting of septic patients had been all but abandoned. Other potential benefits of carboetomidate over etomidate are its inhibition of the 5-HT3 receptor in rat models. Emesis is a complex mechanism of which the 5-HT3 receptor inhibitors are utilized with both central and peripheral effects that reduce nausea and vomiting. Therefore, carboetomidate may have decreased emetogenic properties when compared to etomidate based on its antagonist action at the serotonin receptor.

**Methoxycarbonyl-etomidate**

Methoxycarbonyl-etomidate (MOC-etomidate) is an etomidate derivative that acts on the GABAA receptor and maintains high hypnotic potency, hemodynamic stability, and rapid-onset of action similar to etomidate. MOC-etomidate is a soft analog, or a derivative of etomidate which is designed to undergo rapid and predictable metabolic breakdown (i.e., similar to drugs including remifentanil and esmolol). MOC-etomidate contains a rapidly hydrolyzed ester moiety. The rapid breakdown leads to the metabolite (MOC-ECA), which has adrenocortical inhibitory levels which are 300-400 times lower than that of MOC-etomidate. In rat models, MOC-etomidate was found to not affect corticosterone synthesis following single IV dose. Unfortunately, in prolonged infusions, MOC-ECA metabolites accumulate, leading to a longer time of recovery. This makes MOC-etomidate less than ideal for infusions in the critical care setting.

**Methoxycarbonyl-carboetomidate**

Methoxycarbonyl-carboetomidate (MOC-carboetomidate) is another etomidate derivative which sought to combine the favorable effects of both MOC-etomidate and carboetomidate. By incorporating both structures, the goal was to produce an extremely short duration molecule which would not suppress steroid synthesis. MOC-carboetomidate maintains a short duration of action by ester hydrolysis and maintains the potency of the parent compound, but its duration is longer than that of etomidate in rat models. It possesses no adrenal suppression, thus eliminating the most concerning side effect of etomidate because of its weak affinity for the 11 beta-hydroxylase enzyme. This advantage prevents the consequences of adrenal suppression, thus avoiding many of the side effects that would be detrimental to critically-ill patients. Both MOC-carboetomidate and carboetomidate have similar onset induction times in rat models. The longer duration can be useful when inducing anesthesia and starting a second agent, but may be disadvantageous for longer infusions.

**Cyclopropyl-methoxycarbonyl metomidate and dimethyl-methoxycarbonyl metomidate**

The concern of prolonged hypnosis during longer duration infusions with etomidate derivative MOC-etomidate led to the development of higher potency esters, which are more slowly metabolized with less accumulation of metabolites. This has led to the development of cyclopropyl-methoxycarbonyl metomidate (CPMM) and dimethyl-methoxycarbonyl metomidate (DMMM). CPMM is 10-fold more potent than MOC-etomidate with nearly 100-fold lower metabolite concentrations in rat brain models. CPMM infusions lasting either 5 min or 2 h both exhibit electroencephalogram recovery times of 4 min. Similarly, DMMM infusions of 5 min and 2 h have recovery times of 3 min and 14 min, respectively. Whereas etomidate has a similar 4 min recovery time after 5 min infusion, it has a 31 min recovery time following...
Etomidate fits many of the characteristics of an ideal anesthetic agent. Its rapid onset with rapid clearance and high potency, along with its cardiovascular stability make it a highly desirable anesthetic medication. Unfortunately, it is not ideal for prolonged infusions, and the risk of adrenocortical suppression makes it less than ideal. Seeking to improve on the parent drug, numerous etomidate derivatives have been developed to reduce the shortcomings of etomidate. Etomidate’s adrenocortical suppression was solved by MOC-etomidate, and the concern for MOC-ECA metabolite buildup led to further development of context-insensitive derivatives such as CPMM. It is possible that further testing of the aforementioned derivatives and future development of new derivatives will lead to new anesthetics with improved care and patient safety profiles.

**Conclusion**

A recent *in vivo* CPMM study in beagle dogs confirmed quicker recovery times than those of etomidate, as well as comparable adrenocortical activity profiles to propofol after prolonged infusions. CPMM’s increased potency and decreased metabolite build-up potentially makes it a very favorable drug. In addition, compared with etomidate, CPMM produces lower plasma cytokine concentration and improved survival in lipopolysaccharide inflammatory sepsis models. Thus, CPMM appears to be the best of the current etomidate derivatives for use as a prolonged infusion given its context insensitivity, and may also confer better outcomes in septic patients.

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**Conflicts of interest**

There are no conflicts of interest.

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