Covering letter

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This is in request to an invitation:

'We are the editors for a special issue of the journal “Current Pharmaceutical Design” published by Bentham Science Publishers, Ltd. This special issue will be entitled “Recent Advances in Perioperative Anesthetic Management” and it is our hope that you and any chosen collaborators will be able to contribute an invited comprehensive review for this special issue'

From

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Yours faithfully

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Title Novel etomidate derivatives

Abstract: Etomidate is a well established intravenous anaesthetic agent which has been widely used. Recognised limitation of the agent include adrenocortical suppression, myoclonus and post-operative nausea and vomiting, PONV. MOC-etomidate, carboetomidate and MOC-carboetomidate are novel etomidate derivatives. Their preclinical data and their potential for human administration are critically reviewed. ‘Soft pharmacology (rapid ester hydrolysis) limits the duration of action of MOC-etomidate and MOC-carboetomidate giving
them rapid offset after administration is discontinued. Adrenocortical depression is minimised either by ester hydrolysis or by structural change to the etomidate molecule. Potential limitations include the yet to be determined incidence of myoclonus and PONV if these new agents are administered to humans.

**Keywords:** Etomidate, MOC-etomidate, carboetomidate, MOC-carboetomidate, propofol, midazolam

**Text organization**

**List of abbreviations (if any):** LORR Loss of Righting Reflex

**Conflict of interest (if any) - none**

**Acknowledgements (if any) - none**

**References**

**Appendices**

**Figures/illustrations (if any) three**

**Chemical structures (if any)**

**Tables (if any) one**

**Supportive/supplementary material (if any)**
Novel Etomidate derivatives

Since its introduction into clinical practice in 1972, etomidate has seen widespread use for induction and maintenance of anaesthesia, as well as for intensive care sedation. Potency, rapid onset, short duration of action and especially hemodynamic stability were seen as attractive characteristics to offset its known disadvantages including pain on injection, myoclonus and postoperative nausea and vomiting. Subsequently, concerns about adrenocortical depression following infusion or even bolus doses and their association with excess morality from sepsis\[1, 2\] has restricted its use in the critically ill. Similarly, the superior clinical profile of propofol soon displaced etomidate from routine use in the operating room. Residual etomidate usage is today confined to induction of anaesthesia in haemodynamically unstable patients with non-anaesthesiologist users regarding this as a particular advantage. Dispassionately, at least when used cautiously, propofol can safely be used for both induction and maintenance of anaesthesia in most patients including those with circulatory challenges. Nevertheless there are circumstances such as aortic stenosis where etomidate appears to be superior in haemodynamic terms.[3] Persistent use of etomidate against evidence of propofol (or ketamine) as acceptable alternatives may reflect lack of confidence in managing haemodynamic perturbation by its adherents even though ketamine has been shown to be an acceptable alternative in critically ill patients.[4]

Recently, innovative drug design based on contemporary understanding of etomidate’s mechanism of action and the use of esterase susceptible compounds has brought forward a series of novel etomidate derivatives with clinical potential, Figure 1. This brief review evaluates these compounds and their possible future in anaesthesiology and clinical
medicine. Pre-clinical data for these compounds and for propofol andetomidate are summarised in Table 1.

MOC-etomidate is methoxycarbonyl-etomidate (R)-3-methoxy-3-oxopropyl-(1-phenylethyl)-1H-imidazole-5-carboxylate 11 beta-hydroxylase. MOC-etomidate is anaesthetic in tadpoles and rats where it is less potent than etomidate, ED$_{50}$ for loss of righting response 5.2±1 mg/kg vs 1.00±0.03 mg/kg, mean±SD.[5] MOC-etomidate enhances the activity of GABA at the human GABA$_A$ receptor expressed in *Xenopus* oocytes. The duration of loss of righting was minimally effected by MOC-etomidate dose in contrast to etomidate and propofol where increasing dosage greatly increased the hypnotic response. Single larger bolus doses of twice ED$_{50}$ produced minimal change in mean arterial blood pressure in contrast to etomidate and propofol where hemodynamic disturbance lasted 7 and 12 minutes respectively, however this is probably an unhelpful comparison since the etomidate animals recovered consciousness rapidly whereas hypnosis was prolonged in those receiving etomidate or propofol.[5] MOC-etomidate is lysed by ester hydrolysis with rapid degradation by human liver enzymes. The metabolite MOC-etomidate carboxylic acid arises, Figure 2.

Adreno-cortical suppression. After receiving etomidate, rats pre-treated with dexamethasone showed a markedly attenuated production of corticosterone following ACTH injection whereas those who had received MOC-etomidate or a control infusion did not.[5] The extent of adreno-cortical suppression following MOC-etomidate appears to be of briefer duration or lesser degree than that caused by etomidate.
MOC-etomidate infusions. The different pharmacokinetics and therefore duration of effect of etomidate and MOC-etomidate makes it difficult to directly compare their pharmacodynamic effects. This problem can be addressed using closed-loop computer controlled infusions.[6] When such infusions of MOC-etomidate and etomidate were used to maintain EEG burst suppression ratio of 40% in rats for 15 minutes, the EEG recovery profiles were strikingly different reflecting the rapid hydrolysis of MOC-etomidate and the slower redistribution of etomidate.[7] However, animals anaesthetised with MOC-etomidate showed a persistent low-degree EEG effect long after the initial early recovery. This was hypothesised to be due to accumulated MOC-etomidate metabolites, MOC-etomidate carboxylic acid and methanol. However preliminary experiments infusing MOC-etomidate carboxylic acid failed to produce EEG depression.[7] Subsequent investigations of MOC-etomidate carboxylic acid show that it does activate GABA_A receptors ie it is pharmacologically active.[8] MOC-etomidate carboxylic acid is considerably less potent than MOC-etomidate: EC_{50} for loss of righting response in tadpoles was 2.8±0.64 mM compared to 8±2 μM (mean±SD) for MOC-etomidate carboxylic acid and MOC-etomidate respectively ie. a 350 fold difference in potency.

MOC-etomidate carboxylic acid and adreno-cortical function. MOC-etomidate carboxylic acid suppresses adreno-cortical function.[8] When cultured adreno-cortical cells were stimulated to cause cortisol synthesis, the inhibitory effect of MOC-etomidate carboxylic acid was 300 times weaker than that of MOC-etomidate. So called ‘soft’ drugs[9] ie. those susceptible to rapid esterase hydrolysis are associated with rapid production and potential accumulation of ‘inactive’ metabolites.[10] Given that the concentration of a ‘soft’ drug’s
metabolite may rapidly exceed and become many times greater than that of the parent ‘active’ compound[11], the pharmacology of such metabolites requires detailed scrutiny.[10] Concerns that the product of MOC-etomidate ester hydrolysis may contaminate the ‘clean’ profile of the parent compound appear to have been realised.[7] MOC-etomidate carboxylic acid is both hypnotic (ie it causes EEG depression) and a suppressant of adreno-cortical function.[8] Given the heterogeneity of the human patient population (including as it does those with severe renal and hepatic dysfunction) the suitability of MOC-etomidate for human administration must now be questioned.

Carboetomidate. The depression of adreno-cortical function by etomidate is well established, clinically relevant and serious. Except in special circumstances, such as the infusion of etomidate to manage patients with Cushing’s disease[12], this effect is universally undesirable. In addition to its clinically useful effect at the GABA\textsubscript{A} receptor, etomidate interacts with the heme iron atom at the heart of the 11 beta-hydroxylase enzyme’s active site. This interaction occurs because one of the two nitrogen atoms in etomidate binds to the active site and disrupts it. Carboetomidate is a redesigned etomidate analogue in which the offending nitrogen atom has been replaced by a carbon, Figure 1. This is intended to stop interference with the 11 beta-hydroxylase active site whilst maintaining the GABA\textsubscript{A} receptor mediated hypnotic effect. Carboetomidate is hypnotic in tadpoles and rats with a potency intermediate between those of etomidate and MOC-etomidate (EC\textsubscript{50} for loss of righting reflex in tadpoles 5.4±0.5 µM).[13] When carboetomidate and etomidate were compared in rats using closed-loop computer controlled infusions, the recovery profile from carboetomidate anaesthesia was similar to that of etomidate.[7]
Methoxycarbonyl carboetomidate, MOC-carboetomidate. [13] MOC-carboetomidate adapts the ‘soft’ esterase hydrolysis chemistry of MOC-etomidate and applies it to carboetomidate. MOC-carboetomidate acts at the GABA\(_A\) receptor and is anaesthetic in tadpoles and rats with a similar potency to MOC-etomidate, EC\(_{50}\) for loss of righting in tadpoles 9±1 \(\mu\)M vs 8±2 \(\mu\)M and in rats ED\(_{50}\) 13±5 mg/kg vs 5.2±1 mg/kg, mean±SD, MOC-carboetomidate vs MOC-etomidate respectively. [13] MOC-carboetomidate is rapidly broken down in rat blood, Figure 3.

Etomidate derivatives, adrenocortical depression and sepsis. To what extent have these chemical initiatives resolved the ‘problem’ of adrenocortical depression seen with etomidate? MOC-etomidate certainly impairs adrenocortical function, albeit to a lesser degree than does etomidate. [5] When 30min infusions were given to rats, its effects were intermediate between those of etomidate and an inactive control. [7] Further, the metabolite MOC-etomidate carboxylic acid also has some effects on the adrenocortical system. [8] Thus the pharmacokinetic ‘solution’ to the adrenocortical depression issue is at best unconvincing and at worst failed. Carboetomidate and MOC-carboetomidate are another story. When rats were challenged with lipopolysaccharide they produced an ACTH response that was unaffected by single or repeated bolus doses of etomidate or carboetomidate. [14] Similar changes were noted in the cytokine system. However the production of cortisone was impaired by a bolus of etomidate and profoundly impaired by repeated boluses whereas carboetomidate had no effect. [14] By testing the response to lipopolysaccharide the investigators evaluated the entire adrenocortical system and arguably went further than a simple ACTH test. Carboetomidate therefore appears
convincing as an adrenocortical system sparing anaesthetic agent. Presumably MOC-carboetomidate will have a similar benign effect however this is not yet proved.

What are the obstacles to clinical development of novel etomidate derivatives? Intravenous anaesthesia, sedation and critical care sedation are currently dominated by effective low cost compounds available in generic formulations. Propofol and midazolam are well established although targets for reformulation and new drug development do exist[15]. For propofol, pain on injection, the lipid vehicle and its ability to sustain bacterial growth and the potential for lipid accumulation during prolonged infusion are all undesirable. In the case of midazolam, slow onset, a tendency to accumulation and an active metabolite are potentially problematic. Where do novel etomidate derivatives fit in to this ‘opportunity’?

The attractiveness of etomidate (and by implication of its derivatives) lies in hemodynamic stability. Arguably, rapid onset is already available with propofol and rapid offset can be achieved by low dose propofol combined with remifentanil although slow wake-up remains a problem in critical care sedation using cheaper agents, typically midazolam combined with morphine or fentanyl. If the only advantage of etomidate and its derivatives is haemodynamic stability, then what are their challenges? Etomidate became popular before the introduction of propofol and has been largely superseded by that molecule on the basis of superior clinical performance. Notable disadvantages of etomidate include myoclonus and a tendency to cause postoperative nausea and vomiting, PONV. Excitatory movements in association with intravenous anaesthetics are well known and almost universal however the myoclonic movements seen with etomidate[16] are much greater than the small movements typically associated with propofol.[17] Further, excessive excitation has stalled clinical development of other novel intravenous anaesthetics.[18] Nausea and vomiting are
amongst the most feared complications of anaesthesia and are a major obstacle to the efficient delivery of day surgery. Propofol’s dominance in this scenario was earned not merely by the lack of an emetogenic tendency, rather the drug is itself anti-emetic.[19] It is difficult to see how any anaesthetic agent with a PONV profile similar to etomidate would be acceptable in clinical practice. Etomidate is not water soluble, nor are its novel derivatives. The original drug can be delivered in propylene glycol or a lipid formulation[20] and whilst useful, neither of these represents an improvement on lipid formulated propofol. Further, non-lipid vehicles for propofol remain a target for therapeutic development.[21, 22] alternatives to midazolam are also under development.[23, 24]

Conclusion. MOC-etomidate, carboetomidate and MOC-carboetomidate represent exceptionally innovative approaches to some of the ‘problems’ of etomidate. Their characteristics have been illustrated by a series of well-designed pre-clinical experiments, which clearly illustrate the characteristics (and potential limitations) of these molecules. Whether the ‘advantages’ of these compounds against propofol merit their continued development into man remains uncertain.
Figure 1. Etomidate, MOC-etomidate, carboetomidate and MOC-carboetomidate. Redrawn from[13].
Figure 2. Metabolism of MOC-etomidate. Redrawn from [5]
Figure 3. Metabolism of etomidate, carboetomidate, MOC-etomidate and MOC-carboetomidate in rat blood. Redrawn from[13]
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<td>13.5±5</td>
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<td>*<strong>Inhibition of cortisol production, EC\textsubscript{50} nM</strong></td>
<td>1.3±02</td>
<td>100±20</td>
<td>30000±700</td>
<td>2600±1500</td>
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Table 1. Characteristics of etomidate, etomidate derivatives and Propofol. Data are mean±SD. LORR, Loss of Righting Reflex. *Inhibition of cortisol synthesis by human adrenocortical carcinoma cells. Data derived from[5, 7, 8, 13, 20, 25]
References