CONTRASTING EFFECTS OF ETOMIDATE AND ITS PYRROLE ANALOG CARBOETOMIDATE ON THE ADRENOCORTICAL AND CYTOKINE RESPONSES TO ENDOTOXEMIA

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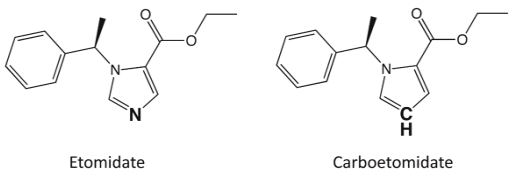
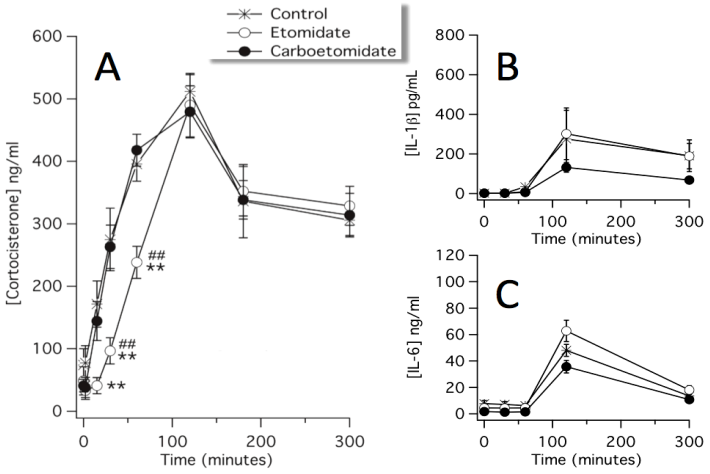
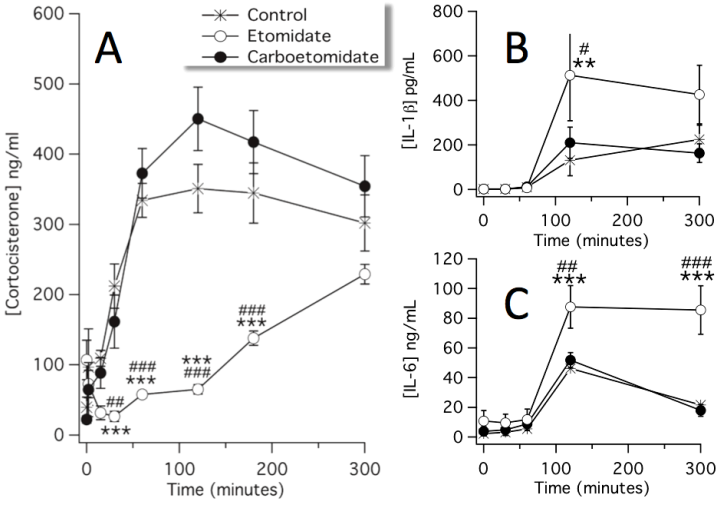
Background: We have developed a novel pyrrole analog of etomidate, (R)-ethyl 1-(1-phenylethyl)-1H-pyrrole-2- carboxylate (carboetomidate), which retains etomidate's desirable anesthetic and hemodynamic properties but lacks its potent inhibitory affect on ACTH-stimulated steroid synthesis (Fig 1). The objective of this study was to test the hypothesis that in contrast to etomidate, carboetomidate neither suppresses the adrenocortical response to endotoxemia nor enhances the accompanying production of pro-inflammatory cytokines.



Methods: For both single and multiple anesthetic dose studies, male Sprague-Dawley rats were injected with Escherichia coli lipopolysaccharide (1 mg/kg) to induce endotoxemia, immediately followed by a hypnotic dose (2x ED50 for loss of righting reflexes) of etomidate, carboetomidate or vehicle alone as a control. For single dose studies, no additional anesthetic (or vehicle) was administered. For multiple anesthetic dose studies, additional doses of anesthetic (or vehicle) were administered every 15 min for a total of eight anesthetic (or vehicle) doses to investigate the impact of prolonged anesthetic administration. Plasma ACTH, corticosterone, and cytokine concentrations were measured before lipopolysaccharide administration and intermittently throughout the 5-hour experiment.



Main Results: In single and multiple anesthetic dose studies, plasma ACTH concentrations were unaffected at any time point by either etomidate or carboetomidate. In single anesthetic dose studies, plasma corticosterone concentrations were briefly (60-120 min) reduced in the etomidate group (Fig 2A) whereas plasma cytokine concentrations were not significantly affected by either anesthetic (Fig 2B & C). However, in multiple anesthetic dose studies, plasma corticosterone concentrations were persistently lower (figure 3A) and peak plasma concentrations of the proinflammatory cytokines IL-1! and IL-6 were higher (figure 3B & C) in the etomidate group versus the carboetomidate and control groups. Peak plasma concentrations of the anti-inflammatory cytokine IL- 10 were similarly elevated in the etomidate and carboetomidate groups versus the control group.



Conclusions: In contrast to etomidate, carboetomidate neither suppresses adrenocortical responsiveness nor enhances pro inflammatory cytokine production in an endotoxemia model of sepsis. These findings suggest that carboetomidate or other structurally related pyrrole etomidate analogs may be useful alternatives to etomidate for maintaining anesthesia in patients with sepsis.