Anesthesiology
1998; 88:1274-80

Etomidate Does Not Alter Recovery after Anoxia of Evoked Population Spikes Recorded from the CA1 Region of Rat Hippocampal Slices

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Background: **Etomidate is an anesthetic agent that reduces the cerebral metabolic rate and causes minimal cardiovascular depression. Its ability to improve recovery after anoxia or ischemia is equivocal. An *in vitro* neuronal preparation was used to examine the action of etomidate on electrophysiologic and biochemical parameters during and after anoxia.**

Methods: **The Schaffer collateral pathway was stimulated, and a postsynaptic evoked population spike was recorded from the CA1 pyramidal cell layer of rat hippocampal slices. Etomidate or propylene glycol, its solvent, was present 15 min before, during, and 10 min after anoxia. Adenosine triphosphate, sodium, and potassium concentrations were measured at the end of anoxia in tissue treated with etomidate, propylene glycol, or with no added drugs.**

Results: **Etomidate did not alter recovery after 6 min of anoxia. The population spikes from untreated slices recovered to 32% of their preanoxic amplitude, and slices treated with 0.5, 3, and 30 μg/ml etomidate recovered to 24%, 35%, and 13%, respectively. Slices treated with propylene glycol, equivalent to that in 3 and 30 μg/ml etomidate, recovered to 46% and 12%, respectively, and this was not significantly different from untreated slices. Etomidate did not attenuate the decrease in adenosine triphosphate concentrations during anoxia. The increase in sodium and the decrease in potassium during anoxia were significantly attenuated by 30 but not by 3 μg/ml etomidate.**

Conclusions: **A range of etomidate concentrations did not significantly alter recovery of the evoked population spike after anoxia in rat hippocampal slices. A high concentration of etomidate did attenuate the increase in sodium and the decrease in potassium during anoxia. (Key words: Cerebral anoxia; cerebral ischemia; intravenous anesthetics.)**

ETOMIDATE is an intravenous anesthetic agent that reduces the cerebral metabolic rate and causes minimal cardiovascular depression, maintaining cerebral perfusion pressure.[1,2] Because reducing the cerebral metabolic rate is a putative neuroprotective mechanism of anesthetic action, Batjer[3] suggested that etomidate might be a good agent for vascular surgery when the cerebral circulation needs to be interrupted. Recent studies have indicated that there is a significant increase in the risk of stroke during cardiovascular and neurosurgical procedures.[4,5] This finding reinforces the need to find anesthetic agents that protect against anoxic and ischemic damage.

Etomidate's protective efficacy has varied in *in vivo* animal studies involving an ischemic insult. Etomidate reduced high-energy phosphate use with severe hypoxia and carotid artery ligation.[6] Low doses of etomidate improved recovery from incomplete cerebral ischemia, but high concentrations significantly hindered recovery.[7] More recent studies found that etomidate improved recovery and reduced extracellular glutamate and dopamine levels after incomplete forebrain ischemia.[8-10] Some studies examining focal ischemia found increased damage with etomidate.[11] Guo *et al.*[12] found moderate temporary improvement from brain stem ischemia after etomidate treatment. Thus the ability of etomidate to protect against ischemia is equivocal.

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Received from the Departments of Anesthesiology and Pharmacology, State University of New York Health Science Center, Brooklyn, New York. Submitted for publication July 28, 1997. Accepted for publication January 13, 1998. Supported by grant GM38866 from the National Institutes of Health to I.S.K. and a grant from the Portuguese American Foundation for Development (FLAD) to M.E.A. Presented in part at the American Society of Anesthesiologists meetings in October 21-25, 1995 and October 19-23 1996.

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We used the rat hippocampal slice to study the effect of etomidate on recovery from anoxic damage. This preparation is independent of the circulation and examines the direct effect of an agent on neurons. We measured biochemical and physiologic parameters from the same region of the brain to identify the mechanism by which an agent acts. In the current study, we examined CA1 pyramidal cells, which are neurons that are extremely sensitive to anoxic and ischemic damage, for their ability to recover electrophysiologic activity after an anoxic insult in the presence of etomidate. We also measured adenosine triphosphate (ATP), sodium, and potassium levels in the hippocampus during anoxia with 3 and 30 μg/ml etomidate.

Materials and Methods

A detailed description of our methods was previously published.[13,14] Adult (aged 110–120 days) male Sprague-Dawley rats (Camm, Wayne, NJ) were used. Approval for the experiments was received from the Animal Care and Use Committee of the State University of New York Health Science Center at Brooklyn. Immediately after decapitation, the brain was removed and placed in ice-cold (2°C), oxygenated artificial cerebrospinal fluid (aCSF). The aCSF contained 126 mM NaCl, 3 mM KCl, 1.4 mM KH_2PO_4, 1.3 mM $MgSO_4$, 1.4 mM $CaCl_2$, 26 mM $NaHCO_3$, 4 mM glucose, *p*H 7.4, and was equilibrated with a gas mixture consisting of 95% oxygen and 5% carbon dioxide. The hippocampi were isolated, cut transversely into 0.5-mm-thick slices, and supported on nylon mesh held in place on a plastic grid in a 7-ml chamber. The temperature of the aCSF in the chamber was increased to 37°C and maintained at this temperature for the rest of the experiment. The slices were submerged 1 cm below the surface of the aCSF, which was exchanged at a rate of 60 ml/min. The aCSF was aerated with 95% oxygen and 5% carbon dioxide.

Electrophysiologic Experiments

Slices were allowed 1 h of undisturbed superfusion for stabilization after dissection; the aCSF was aerated with 95% oxygen and 5% carbon dioxide. At the end of the hour, a stimulating electrode was placed in the presynaptic Schaffer collateral pathway and a tungsten recording electrode was positioned in the CA1 pyramidal cell layer. The Schaffer collateral pathway was stimulated by a supermaximal biphasic pulse every 10 s throughout the rest of the experiment; this evoked a postsynaptic population spike in the CA1 pyramidal cell layer. Etomidate (Amidate; Abbott Laboratories, Chicago, IL) was added to the aCSF superfusing the slices 15 min before anoxia. Anoxia was generated by changing the superfusing aCSF to one that was preequilibrated with 95% nitrogen and 5% carbon dioxide for 6 min. The aCSF was aerated with 95% oxygen and 5% carbon dioxide; after 10 min, the aCSF was changed to a solution that did not contain etomidate. Control experiments were done without any drug and with propylene glycol, the solvent in the clinical formulation of etomidate. Propylene glycol was prepared as a 35% vol/vol solution, its concentration in the clinical formulation of etomidate, and the same volume of that solution as the clinical etomidate solution was added to the preparations. The population spike was then observed for an additional 60 min after anoxia. Recovery was calculated by dividing the 1-h postanoxic population spike amplitude by the preanoxic, predrug population spike amplitude.

Biochemical Experiments

For biochemical studies, rat hippocampal slices were obtained as described previously. Grids with slices obtained from the same animal were placed in separate beakers containing aCSF that were aerated with a gas mixture of 95% oxygen and 5% carbon dioxide and maintained at 37°C. Anoxia was generated by replacing the oxygen gas mixture abruptly with a mixture of 95% nitrogen and 5% carbon dioxide for 6 min. The time course of the biochemical experiments matched those described for the electrophysiologic studies. Either etomidate, propylene glycol, or no drug was added to the aCSF for 15 min before and during anoxia.

The ATP was measured in individual slices incubated as described previously. For these experiments, a 6-min anoxia period was examined. After anoxia, or an equivalent time period, the slices were removed from the beaker, rapidly frozen in liquid nitrogen, lyophilized, and the CA1 regions were dissected and weighed.[13] The ATP was then extracted by homogenizing the tissue in 3N ice-cold perchloric acid and measured, after neutralization, using the firefly luciferin-luciferase assay.[15]

Sodium and potassium levels were measured from whole hippocampal slices after 6 min of anoxia. The slices were treated as described before until the end of the experimental period, when they were removed

Table 1. Recovery of the Evoked Population Spike 60 min after 6 min of Anoxia

Drug	% Recovery (6 min of anoxia)	n
Untreated	32 ± 37	13
Etomidate (clinical formulation)		
0.5 μg/ml	24 ± 38	6
3 μg/ml	35 ± 46	6
30 μg/ml	13 ± 32	6
Propylene glycol 35% vol/vol (equivalent to amount in clinical formulation of etomidate)		
1.5 ml/L (equivalent to 3 μg/ml)	46 ± 34	4
15 ml/L (equivalent to 30 μg/ml)	12 ± 19	8

Values are mean ± SD. No groups were significantly different from the untreated anoxic group.

from the beakers and submerged in agitated ice-cold (4°C) isotonic sucrose for 10 min. This permitted the washout of ions from the extracellular space while minimizing the loss of intracellular ions.[13] The slices were removed from the sucrose, placed in preweighed microcentrifuge tubes, dried at 90°C for 48 h, and weighed again. After the tissue was shaken for 18 h with dilute nitric acid (0.1 N), the supernatant was assayed using a Radiometer (Copenhagen, Denmark) FLM3 flame photometer.

All values are expressed as mean ± SD. The number of animals in each group is given in the tables and figures. Statistical analysis was performed using analysis of variance and two-tailed unpaired Student's *t* tests. Probability values <0.05 were considered significant. The Prism (version 2) computer program (GraphPad Software, San Diego, CA) was used for all statistical calculations.

Results

Recovery of the Evoked Population Spike

Etomidate (0.5, 3, and 30 μg/ml) did not increase the latency or decrease the amplitude of the evoked population spike recorded in the CA1 pyramidal cell layer of rat hippocampal slices. The latency was 101 ± 2%, 102 ± 3%, and 103 ± 2% of its predrug latency after 0.5, 3, and 30 μg/ml etomidate. The amplitude of the response after 0.5, 3, and 30 μg/ml etomidate was 100 ± 4%, 99 ± 6%, and 98 ± 8% of its predrug amplitude.

The postsynaptic population spike recovered to 32% of its preanoxic amplitude in untreated slices subjected to 6 min of anoxia (table 1). The response recovered to 24% of its preanoxic amplitude in slices treated with 0.5 μg/ml etomidate (clinical formulation) before, during, and after 6 min of anoxia. Increasing the etomidate concentration to 3 or 30 μg/ml did not significantly alter the recovery of the evoked response (table 1). There was no significant change of the postsynaptic population spike at any concentration of etomidate. Figure 1 shows typical recordings from this experiment examining 3 μg/ml etomidate.

The clinical formulation of etomidate contains 35% vol/vol propylene glycol. We investigated the effect of this solvent, without etomidate, on recovery after 6 min of anoxia. The amplitude of the evoked response returned to 46% and 12%, respectively, after 6 min of anoxia with a propylene glycol concentration equivalent to that in the 3 and 30 μg/ml clinical formulation of etomidate. These values were not significantly different from untreated slices.

Adenosine Triphosphate

The concentration of ATP was measured in the CA1 region of rat hippocampal slices at the end of anoxia. The concentration of ATP in this region of untreated normoxic slices was 5.1 nmol/mg dry weight. After 6 min of anoxia, the ATP concentration decreased to 47% of its normoxic concentration (table 2). The clinical formulation of etomidate did not significantly alter the decrease in ATP during anoxia. The ATP level decreased to 49% after 6 min of anoxia with 3 μg/ml etomidate and to 51% with 30 μg/ml etomidate. Propylene glycol alone, at a concentration equivalent to that in 30 μg/ml etomidate, also did not significantly alter the decrease in ATP after 6 min of anoxia (47%).

Sodium and Potassium Ions

The concentrations of sodium and potassium were measured from whole hippocampal slices. The sodium concentration in untreated normoxic slices was 133 nmol/mg dry weight; at the end of 6 min of anoxia, the sodium increased to 135% of this concentration (table 3). The lower concentration of etomidate (3 μg/ml) did not significantly alter this increase (133%), but 30 μg/ml etomidate significantly reduced the increase in sodium during anoxia to 114% of its normoxic concentration. Propylene glycol, in a concentration equivalent to that

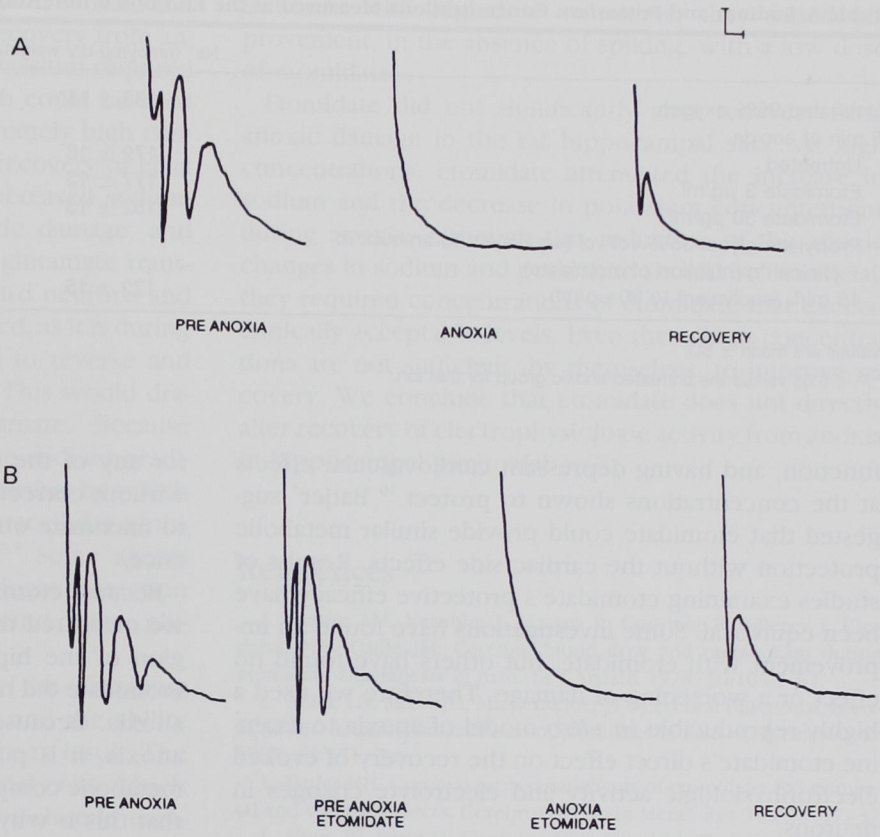

Fig. 1. The effect of etomidate on recovery of CA1 pyramidal cells after anoxia. (*A*) The evoked population spike due to stimulation of the Schaffer collateral pathway is recorded from the CA1 pyramidal cell layer of untreated hippocampal slices. The responses are shown before anoxia, during 6 min of anoxia, and 60 min after reoxygenation. (*B*) Slices were exposed to 3 μg/ml etomidate 15 min before, during, and 10 min after a 6-min anoxic period. Evoked population spikes, recorded as in panel A, are shown before etomidate (preanoxia), after etomidate before anoxia, during anoxia with etomidate, and 60 min after anoxia (50 min after etomidate washout). The scale applies to all traces. Scale, 250 μV; 2 ms.

achieved with the 30 μg/ml etomidate treatment, did not significantly alter the increase in sodium (129%).

The potassium concentration in untreated normoxic slices was 149 nmol/mg dry weight; at the end of 6 min of anoxia, the potassium decreased to 82% of this concentration. Although 30 μg/ml etomidate significantly reduced the decrease in potassium to 95% of its normoxic concentration, 3 μg/ml etomidate had no significant effect (83%) (table 3). Propylene glycol (equivalent to that in 30 μg/ml etomidate) did not significantly alter the decrease in potassium (78%).

Table 2. Adenosine Triphosphate (ATP) Concentrations Measured at the End of a 6 min Anoxic Period

	ATP (nmol/mg dry wt)	n
Untreated 95% oxygen	5.1 ± 0.6*	23
6 min of anoxia		
Untreated	2.4 ± 0.7	23
Etomidate 3 μg/ml	2.6 ± 0.5	24
Etomidate 30 μg/ml	2.7 ± 0.6	24
Propylene glycol 35% vol/vol (equivalent to amount in clinical formulation of etomidate)		
15 ml/L (equivalent to 30 μg/ml)	2.4 ± 0.6	24

Values are mean ± SD.

* $P < 0.05$ *versus* the untreated anoxic group.

Discussion

Anesthetic agents that improve recovery from neuronal damage are highly desirable for surgical procedures for which there is a risk of ischemia and anoxia. Recent studies indicate that in addition to neurosurgical procedures, carotid endarterectomy and surgery with cardiopulmonary bypass subject the patient to a greater risk of stroke in the perioperative period.[4,5] Thiopental has been shown to improve recovery after cardiopulmonary bypass but has the disadvantages of being slowly eliminated, delaying recovery of central nervous system

Table 3. Sodium and Potassium Concentrations Measured at the End of a 6 min Anoxic Period

	Na^+ (nmol/mg dry weight)	K^+ (nmol/mg dry weight)	n
Untreated 95% oxygen	133 ± 15*	149 ± 6*	6
6 min of anoxia			
Untreated	179 ± 18	122 ± 9	5
Etomidate 3 μg/ml	177 ± 13	124 ± 8	6
Etomidate 30 μg/ml	152 ± 13*	142 ± 13*	6
Propylene glycol 35% vol/vol (equivalent to amount in clinical formulation of etomidate)			
15 ml/L (equivalent to 30 μg/ml)	172 ± 15	116 ± 9	6

Values are mean ± SD.

* $P < 0.05$ *versus* the untreated anoxic group for that ion.

function, and having depressant cardiovascular effects at the concentrations shown to protect.[16] Batjer[3] suggested that etomidate could provide similar metabolic protection without the cardiac side effects. Results of studies examining etomidate's protective efficacy have been equivocal. Some investigations have found an improvement with etomidate, but others have found no effect or a worsening of damage. Therefore we used a highly reproducible *in vitro* model of anoxia to examine etomidate's direct effect on the recovery of evoked electrophysiologic activity and electrolyte changes in neurons.

Plasma concentrations 1 min after a bolus dose of 0.3 mg/kg etomidate approximate 0.48 – 2.6 μg/ml,[17] whereas 3 μg/ml causes a 45% reduction in the cerebral metabolic rate for oxygen.[1] We examined etomidate concentrations of 0.5 and 3 μg/ml, which approximate these clinical concentrations and 30 μg/ml, a concentration that is 10 times the clinical concentration. However, if we account for the 90% bound etomidate to protein in plasma,[17] then our concentrations are approximately 10 times higher than the concentration of free etomidate in plasma. Thus our lowest concentration of etomidate, 0.5 μg/ml, is most similar to the clinically used dose, and 30 μg/ml is 100 times the clinical dose.

Etomidate did not increase the latency or reduce the amplitude of the evoked postsynaptic population spike before anoxia. This is similar to the lack of effect of etomidate on brain stem auditory evoked potentials in humans.[12] Visual evoked potentials demonstrate a slight increase in latency with no change in amplitude.[18] The clinical formulation of etomidate, which is dissolved in propylene glycol, did not alter recovery. We found no significant effect of propylene glycol alone. Our studies found no significant difference in physiologic recovery for any of the etomidate groups, even when a *t* test without correction for multiple comparisons was used to maximize our chance of finding a significant difference.

Because etomidate is thought to suppress metabolism, we measured the concentration of ATP in the CA1 region of the hippocampal slice at the end of anoxia. Etomidate did not attenuate the decrease in ATP during anoxia. Because neurons reduce their activity during anoxia, it is possible that etomidate affects the same metabolic components that are inhibited by anoxia and that this is why it does not further attenuation the decrease of ATP during anoxia. A major component of ATP use in neurons is the sodium-potassium ATPase pump; reducing sodium influx should reduce pump activity and thereby preserve ATP levels. We found this result with the sodium channel blockers tetrodotoxin and lidocaine[19,20]; it is unclear why 30 μg/ml etomidate, which reduced sodium influx during anoxia, did not improve ATP concentrations.

Clinically relevant concentrations of etomidate[1,17] (0.5 and 3 μg/ml) did not attenuate the increase in sodium or the decrease in potassium during anoxia. This correlates with the lack of physiologic protection. However, an extremely high concentration of etomidate (30 μg/ml), which also did not alter electrophysiologic recovery, significantly reduced the anoxic changes in sodium and potassium. This suggests that reducing the changes of these ions during anoxia is not sufficient to impart physiologic protection. We previously showed that 10 μM lidocaine and 600 nM tetrodotoxin attenuate the anoxic changes in sodium and ATP and improve recovery.[19,20] These results suggest that in addition to attenuating the changes in sodium, it is important to alter other parameters during anoxia such as ATP.

The attenuation of the anoxic changes in sodium and potassium could potentially improve recovery from anoxia, but this effect on sodium and potassium required a concentration many times that which could be used clinically. In addition, even at this extremely high concentration we found no effect on the recovery of electrophysiologic activity after anoxia. Increased sodium influx is an important factor in anoxic damage, and blocking it should be beneficial. The glutamate transporter moves glutamate and sodium into neurons and glia; when the sodium gradient is reduced, as it is during ischemia, this pump has been shown to reverse and transport glutamate out of the cells.[21] This would dramatically increase extracellular glutamate. Because etomidate improves preservation of the sodium gradient during anoxia, this may be the mechanism by which it attenuates the large increase in extracellular glutamate and dopamine during ischemia.[8,9] Some agents currently being examined for pharmacologic protection during ischemia block sodium channels and reduce glutamate release.[22]

The hippocampal slice is a good model for examining the direct effect of agents on neurons and the ability of these agents to improve recovery after an insult. The hippocampus contains the CA1 pyramidal cells, which are extremely sensitive to anoxic and ischemic damage.[23] Because in this model the neurons are directly superfused independent of the vasculature, any effects seen are independent of cerebral perfusion and blood flow redistribution. Thus this model only examines the effects of drug directly on these neurons, and it cannot examine the effects of agents on systemic parameters or neuronal circuits not contained entirely in the hippocampus. Our studies were performed under physiologic conditions; the temperature was maintained at 37°C, the glucose concentration was 4 mM, and the divalent cation concentrations were 1.4 mM calcium and 1.3 mM magnesium. All of these factors influence anoxic damage, neuronal activity, or both, so it is important that they closely match conditions *in vivo*.

Our data suggest that etomidate neither increases nor decreases the degree to which induced electrophysiologic activity recovers after an anoxic insult. This suggests that the increased damage with etomidate seen in the middle cerebral artery occlusion model of ischemia is due to a global action of the drug and not to its deleterious effect on individual neurons.[11] Baughman *et al.*[7] found an increase in electroencephalographic spiking and a worse outcome after incomplete cerebral ischemia with high-dose etomidate; they found improvement, in the absence of spiking, with a low dose of etomidate.

Etomidate did not significantly alter recovery from anoxic damage in the rat hippocampal slice. At high concentrations, etomidate attenuated the increase in sodium and the decrease in potassium concentrations during anoxia. Although this reduction of the anoxic changes in sodium and potassium should be beneficial, they required concentrations of etomidate that exceed clinically acceptable levels. Even these high concentrations are not sufficient, by themselves, to improve recovery. We conclude that etomidate does not directly alter recovery of electrophysiologic activity from anoxia in hippocampal pyramidal cells.

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