Enhancement of Somatosensory Evoked Potentials by Etomidate in Cats: An Investigation of Its Site of Action

Satwant K. Samra, M.D.,* Linda S. Sorkin, Ph.D.†

Enhancement of somatosensory evoked potentials by etomidate has been reported in recent clinical studies. This investigation was designed to investigate the central nervous system site of action responsible for this effect. Six adult cats were anesthetized with halothane (0.8–1%) in a mixture of 50% N₂O in O₂. A recording electrode was placed stereotactically in the ventral posterior lateral nucleus of thalamus (VPL), and a ball electrode was placed over the surface of the hind limb region of primary sensory cortex. Somatosensory evoked potentials in response to stimulation of tibial nerve thus were simultaneously recorded from cerebral cortex and VPL. The effect of two doses (1 and 3 mg·kg⁻¹) of etomidate given 2 h apart on the latency and amplitude of cortical (positive wave at 15 ms) and thalamic (positive deflection at 10 ms, followed by negative deflection at 17 ms) evoked potentials was studied. There was no significant effect of etomidate on either latency or amplitude of early, positive thalamic potentials. Both doses of etomidate caused a significant increase in the latency and amplitude of cortical potentials. The mean latency of cortical potential increased by 1.72 ms (11%) after the 1 mg·kg⁻¹ dose and 2.3 ms (15.9%) after the 3 mg·kg⁻¹ dose. The maximum mean increase in the amplitude of cortical potentials was 14.3 μV (mean increase 78%, range 28–241%) after 1 mg·kg⁻¹ and 19.1 μV (mean increase 112%, range 28–202%) after 3 mg·kg⁻¹. Cortical amplitude remained significantly elevated for 30 min after 1 mg·kg⁻¹ and for the remainder of the study period (60 min) after 3 mg·kg⁻¹. Etomidate affected the late thalamic potential (a negative potential with a latency of 17 ms) less than it did the cortical waveform. Late thalamic amplitude increased by a maximum of 50 and 53% after 1 and 3 mg·kg⁻¹, respectively. Changes in the latency of the negative thalamic potential were not statistically significant. We conclude that enhancement of somatosensory evoked potentials by etomidate is due to the effect of etomidate on the cerebral cortex rather than a mediation through subcortical structures. (Key words: Anesthetics, intravenous. Etomidate: site of action. Monitoring: somatosensory evoked potentials.)

IN CONTRAST to most of the currently used inhalation and intravenous anesthetics that are known to prolong the latency and decrease the amplitude of somatosensory evoked potentials (SSEPs), etomidate has been shown to increase the amplitude of SSEPs.1–4 The site of SSEP enhancement within the central nervous system has not been systematically investigated, although one author has mentioned disinhibition of subcortical structures as a possibility.4 However, clinical investigations2,5 dealing with the effect of etomidate on median nerve SSEPs have shown that only the cortical component of SSEPs is enhanced. Components of SSEPs with neural generators in the spinal cord are unaffected. This pattern suggests that etomidate's site of action is somewhere between the high spinal cord and sensory cortex. Human brain stem auditory evoked responses are unchanged after intravenous administration of etomidate,5 a finding that suggests a lack of effect of etomidate at the subcortical level. We designed this investigation to further elucidate the site of action of this effect by simultaneously recording of SSEPs from the primary sensory cortex and the ventral posterior lateral nucleus of thalamus (VPL), which is the highest relay station for peripheral sensory input to the brain.6 Our results indicate that the primary site of action of this effect of etomidate upon SSEPs is the cerebral cortex rather than the subcortical structures, as previously proposed.

Materials and Methods

Experiments were conducted in accordance with the standards approved by the Animal Use Committee at our institution. Six adult cats weighing 3.5–4.0 kg were anesthetized with halothane in a mixture of 50% N₂O in O₂. Surgical preparation included a tracheostomy to facilitate mechanical ventilation, cannulation of the femoral artery for continuous monitoring of arterial pressure, peripheral venous access for administration of drugs, and isolation of the tibial nerve for peripheral stimulation. A small craniotomy exposed the primary sensory cortex and adjacent area of the brain and thereby provided access to the thalamus. At the conclusion of surgical preparation, the animal was placed in a prone position with the head fixed in a stereotactic frame.

Muscle paralysis was achieved by administration of pancuronium bromide and mechanical ventilation was adjusted to maintain a steady end-tidal CO₂ tension between 26 and 30 mmHg. Rectal temperature was monitored continuously and maintained at 37° C with the aid of a heating blanket controlled by a servomechanism. A pair of silver hook stimulating electrodes were placed under the tibial nerve. A ball electrode was placed on the

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hind limb region of the primary somatosensory cortex and a stainless steel monopolar recording electrode was introduced stereotactically into the VPL. Stereotactic coordinates used were A8 and ML7, as described by Berman and Torres. The final positions of the recording electrodes were adjusted to obtain evoked potentials of maximal amplitude. Evoked potentials in response to 50 square-wave impulses of 200-μs duration with a frequency of 0.5 Hz were recorded with a band pass of 10–10,000 Hz.

Once the optimal recording sites were identified, the exposed cerebral cortex as well as the tibial nerve were covered with a warm solution of mineral oil and petroleum jelly to prevent heat loss and desiccation of nervous tissue. Stimulation and recording parameters were held constant throughout each experiment. After maintenance of a steady state of anesthesia (0.8–1% halothane in 50% N₂O and O₂) and ventilation for at least 2 h and at least 30 min after stereotactic placement of thalamic electrode, control SSEPs were recorded simultaneously from the sensory cortex and VPL after stimulation of the tibial nerve.

Etomidate 1 mg·kg⁻¹ then was given intravenously and evoked potentials were recorded after 5, 10, 15, 20, 30, 40, 50, and 60 min. After a 1-h recovery period, control SSEPs were recorded again. Subsequently, a second dose of etomidate (3 mg·kg⁻¹) was given and a second set of records obtained at the same time intervals. Two replications of evoked responses to 50 stimuli were averaged at each time point with a two-channel signal averager (Nicolet, Madison, WI). Values for amplitude and latency reported are the mean of both replications in each animal. All data were stored for analysis at a later time.

After completion of evoked potential recording, a lesion was made at the thalamic recording site by passing a 20-μA current for 20 s through the thalamic electrode. At the conclusion of the experiments, the animals were killed by an intravenous injection of KCl. The brain was removed immediately and was stored overnight in 10% formalin buffer solution with potassium ferrocyanide to stain the iron deposit around the thalamic lesion. The next morning, the brain was transferred to a 30% sucrose solution in 10% formalin for cryoprotection. At a later date, 50-μm sections of the frozen brain were cut and stained with neutral red, and the thalamic recording site was confirmed.

**DATA ANALYSIS**

The points for measurements of amplitude and latency in our study are shown in figure 1. Values of latency are reported in milliseconds and those for amplitude in microvolts. Changes in amplitude also were normalized as a percentage change from the control traces, which were considered to be 100%. Numerical data thus obtained were analyzed by a two-way analysis of variance for repeated measurements to evaluate the main effect of the etomidate dose and of time. When this test revealed a significant effect \( P < 0.05 \), *post hoc* testing was performed with Tukey’s analysis for multiple comparisons. Thus, values of latency and amplitude at all time points were compared to control values to determine the time course of any significant effect of the two doses of etomidate.

**Results**

Administration of etomidate caused a transient dose-related decrease in mean arterial blood pressure, which returned to control values within 2–3 min. The effect of etomidate on thalamic and cortical evoked potentials in a representative animal is shown in figure 2. In general, cortical evoked potentials showed a marked dose-related increase in the amplitude, accompanied by a small increase in latency. Amplitude and latency of the positive thalamic potential remained unaffected, whereas the amplitude of
TABLE 1. Effect of Etomidate on Latency of Cortical and Thalamic Evoked Potentials

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Cortical Potentials</th>
<th>Thalamic Potentials</th>
<th>Positive Wave</th>
<th>Negative Wave</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Etomidate 1 mg/kg</td>
<td>Etomidate 3 mg/kg</td>
<td>Etomidate 1 mg/kg</td>
<td>Etomidate 3 mg/kg</td>
</tr>
<tr>
<td>Control</td>
<td>14.86 ± 1.05</td>
<td>14.66 ± 0.78</td>
<td>9.86 ± 0.27</td>
<td>9.72 ± 0.30</td>
</tr>
<tr>
<td>5</td>
<td>16.48 ± 1.71†</td>
<td>16.99 ± 1.43†</td>
<td>9.92 ± 0.31</td>
<td>9.97 ± 0.56</td>
</tr>
<tr>
<td>10</td>
<td>16.58 ± 1.97†</td>
<td>16.95 ± 1.37†</td>
<td>9.91 ± 0.32</td>
<td>10.07 ± 0.38</td>
</tr>
<tr>
<td>15</td>
<td>16.37 ± 2.19†</td>
<td>16.84 ± 1.41†</td>
<td>9.90 ± 0.32</td>
<td>10.11 ± 0.34</td>
</tr>
<tr>
<td>20</td>
<td>16.30 ± 2.14†</td>
<td>17.00 ± 1.73†</td>
<td>9.99 ± 0.33</td>
<td>10.16 ± 0.56</td>
</tr>
<tr>
<td>30</td>
<td>16.50 ± 2.78†</td>
<td>16.82 ± 1.59†</td>
<td>9.88 ± 0.34</td>
<td>10.24 ± 0.48</td>
</tr>
<tr>
<td>40</td>
<td>14.95 ± 0.86</td>
<td>16.35 ± 1.58†</td>
<td>9.86 ± 0.32</td>
<td>10.23 ± 0.49</td>
</tr>
<tr>
<td>50</td>
<td>14.70 ± 0.74</td>
<td>16.44 ± 1.41†</td>
<td>10.04 ± 0.43</td>
<td>10.21 ± 0.51</td>
</tr>
<tr>
<td>60</td>
<td>14.70 ± 0.75</td>
<td>16.18 ± 1.72†</td>
<td>9.83 ± 0.32</td>
<td>10.10 ± 0.34</td>
</tr>
</tbody>
</table>

ANOVA: P = 0.0112

† Significant differences compared to control value (Tukey's analysis).

* Means ± SD.

the negative afterpotential in thalamic recordings was increased.

As is well known to occur in SSEP monitoring, the amplitude of cortical evoked potentials showed a marked interanimal variation. Control values (mean ± SD) for amplitude were 18.9 ± 6.7 μV (range 11.9–28.5) before 1 mg · kg⁻¹ and 18.6 ± 6.0 μV (range 11.2–26.5) before 3 mg · kg⁻¹. Latency was more consistent across all animals in control recordings (table 1). Amplitude of the cortical evoked potential increased in every animal after the administration of etomidate, but the degree of this enhancement, too, varied from animal to animal. Maximum increase in amplitude was seen 10 min after injection of etomidate when values (mean ± SD) were 33.3 ± 10.6 μV (range 16.4–45.6) after 1 mg · kg⁻¹ and 37.8 ± 14.3 (range 23.0–65.9) after 3 mg · kg⁻¹ (table 2). Therefore, we normalized the numerical data relating to amplitude, such that the preetomidate recordings in each animal served as controls (100%).

Figures 3 and 4 show the time course of mean changes in normalized amplitude of cortical and thalamic potentials. Etomidate caused an increase in the amplitude of cortical evoked potentials after both doses. This effect was apparent in the 5-min recordings, and the peak effect was seen in the 10-min recordings. At this point, the mean amplitude after 3 mg · kg⁻¹ was 212% (range 128–302%) and after 1 mg · kg⁻¹ was 178% (range 128–341%). Two-way analysis of variance revealed a significant effect of

**TABLE 2. Effect of Etomidate on Amplitude of Cortical and Thalamic Evoked Potentials**

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Cortical Potentials</th>
<th>Thalamic Potential</th>
<th>Positive Wave</th>
<th>Negative Wave</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 mg/kg</td>
<td>3 mg/kg</td>
<td>1 mg/kg</td>
<td>3 mg/kg</td>
</tr>
<tr>
<td>Control</td>
<td>18.96 ± 6.7</td>
<td>18.63 ± 6.0</td>
<td>99.30 ± 48.6</td>
<td>81.73 ± 43.1</td>
</tr>
<tr>
<td>5</td>
<td>29.82 ± 10.0*</td>
<td>36.85 ± 16.3*</td>
<td>89.44 ± 44.3</td>
<td>86.04 ± 42.4</td>
</tr>
<tr>
<td>10</td>
<td>32.25 ± 10.6*</td>
<td>35.78 ± 14.3*</td>
<td>90.66 ± 46.1</td>
<td>83.00 ± 43.1</td>
</tr>
<tr>
<td>15</td>
<td>31.96 ± 8.5*</td>
<td>36.55 ± 16.7*</td>
<td>96.58 ± 45.1</td>
<td>85.59 ± 46.6</td>
</tr>
<tr>
<td>20</td>
<td>29.28 ± 8.4*</td>
<td>34.30 ± 13.9*</td>
<td>97.57 ± 47.4</td>
<td>84.29 ± 44.2</td>
</tr>
<tr>
<td>30</td>
<td>25.94 ± 5.3*</td>
<td>31.47 ± 11.0*</td>
<td>94.74 ± 51.3</td>
<td>84.63 ± 48.7</td>
</tr>
<tr>
<td>40</td>
<td>23.95 ± 7.0</td>
<td>30.15 ± 9.2*</td>
<td>92.06 ± 48.3</td>
<td>80.74 ± 47.4</td>
</tr>
<tr>
<td>50</td>
<td>22.42 ± 5.4</td>
<td>30.87 ± 13.5*</td>
<td>89.93 ± 47.5</td>
<td>82.22 ± 46.7</td>
</tr>
<tr>
<td>60</td>
<td>19.08 ± 6.3</td>
<td>28.49 ± 6.6*</td>
<td>90.93 ± 49.4</td>
<td>81.94 ± 48.9</td>
</tr>
</tbody>
</table>

ANOVA: P = 0.0004

P = 0.7459

0.0003

Means ± SD.

* Significant difference compared to control value (Tukey's analysis).
time ($P = 0.0004$) but the difference between the two doses of etomidate was not significant ($P = 0.27$). When compared to control values, a significant increase in amplitude persisted for 30 min after 1 mg·kg$^{-1}$ dose, after which there was a gradual return toward control values. The increase in amplitude after 3 mg·kg$^{-1}$ persisted throughout the study period. The amplitude of the positive thalamic potentials did not show a significant change ($P = 0.75$) after either dose of etomidate (fig. 3), whereas amplitude of the negative thalamic potential increased in a manner similar to that of cortical potentials (fig. 4). The maximum mean amplitude of the negative thalamic wave was 149.5% after 1 mg·kg$^{-1}$ etomidate, seen in the 5-min recordings, whereas that for the 3 mg·kg$^{-1}$ dose was 168.4% (range 124–215%) seen after 10 min. This significant increase in amplitude persisted for the duration of the study after the 3 mg·kg$^{-1}$ dose, but after the 1 mg·kg$^{-1}$ dose it returned toward control values after 20 min. The observed values of amplitude in microvolts are shown in table 2.

Table 1 shows the changes in latency of cortical and thalamic evoked potentials. There was a significant ($P = 0.01$) increase in the latency of cortical evoked potentials. This increase was apparent 5 min after both doses and persisted for 30 min after 1 mg·kg$^{-1}$ and for the entire duration of the experiment after 3 mg·kg$^{-1}$. In contrast, the latency of positive thalamic potentials remained unchanged ($P = 0.84$). The mean latency of the negative thalamic potential increased by 0.8 ms after the 1 mg·kg$^{-1}$ dose and returned toward control values after 30 min, whereas the 3 mg·kg$^{-1}$ dose resulted in a mean increase of 1.8 ms in latency that persisted for the duration of the experiment. Changes in latency of the negative thalamic potential were not significant ($P = 0.08$).

**Discussion**

The aim of this investigation was to determine the site in the central nervous system at which enhancement of cortical evoked potentials by etomidate occurs. Previous reports dealing with neural generators of SSEPs$^6$–$^10$ have suggested that the cervical spinal cord potential ($N_{14}$) originates in the dorsal column nuclei and medial lemnicus, whereas $N_{90}$ originates either in the sensory cortex or thalamocortical radiation. Previous clinical studies$^2$–$^3$ have shown that etomidate increases the amplitude of $N_{90}$ but does not change $N_{14}$. In the current study, we chose to record SSEPs from the VPL because it is the last neuronal relay for sensory information prior to its arrival at the sensory cortex, and hence is the ideal anatomic location to differentiate between drug effects on primary sensory cortex and subcortical structures.

There are few data on the recommended dose of etomidate for induction of anesthesia in cats. Doses of etomidate used in our study were based on those recommended for dogs$^{13}$ and were three to ten times the dose recommended for humans. Hemodynamic stability typifies induction of anesthesia with etomidate in clinical practice, and yet we noted a transient decrease in blood pressure in most of the animals. This may be the result of the relatively large dose of etomidate used in our study. In all animals, blood pressure returned to control values before the first set of evoked potentials was recorded. Therefore, we believe that hemodynamic changes in our study did not affect SSEPs.

We found an increase in the amplitude of cortical evoked potentials along with a slight increase in the latency of this component, in agreement with the data reported on humans.$^1$–$^3$ In previous studies, larger increases in am-
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amplitude were reported by McPherson et al.2 (50–300%), Kochs et al.1 (100–1,100%), and Koht et al.3 (up to 400%); in our study, however, this increase was less marked (mean 112%, range 28–202%). One explanation for this difference is that in the clinical studies cited above, evoked potentials were recorded immediately after induction of anesthesia with etomidate, and no other anesthetic drugs were used. In our study, animals were anesthetized with halothane and N2O for more than 2–3 h prior to administration of etomidate. Both halothane and N2O are known to reduce the amplitude of cortical evoked potentials.14–16 Therefore, it is likely that in our experiments, use of inhalation anesthetics somewhat masked the effect of etomidate.

Etomidate produced no effect on either amplitude or latency of the positive thalamic potential, whereas the negative thalamic afterpotential showed changes in latency and amplitude similar to those of the cortical potentials. Our finding of a lack of significant change in either amplitude or latency of the positive thalamic potential suggests that etomidate does not have a significant effect on either the peripheral sensory pathway or subcortical relays of afferent somatosensory information within the brain. In a study of auditory evoked responses, Thornton et al.5 found that etomidate had no effect on brain stem responses, but recorded a depressant effect on middle latency (early cortical) auditory responses. The latter contrasts with etomidate’s known amplitude-enhancing effect on cortical SSEP waveforms, as seen in the current study, and indicates that this drug affects cortical tissue in a heterogeneous manner.

In control recordings, negative thalamic waves had a mean latency of 16.7 ms following the cortical evoked potential (mean latency of 14.9 ms). Striking similarity in the changes in latency and amplitude of negative thalamic wave and cortical potentials suggests that changes in the thalamic negative wave may be secondary to the cortical effect. This interpretation is consistent with the concept of the monosynaptic thalamocortical–corticothalamic loop that has been suggested by some investigators.17 Had the changes in the thalamic negative wave been due to the direct effect of etomidate at the level of the thalamus, we would have seen changes in the latency and amplitude of the positive thalamic wave representing arrival of afferent sensory input at VPL.

In conclusion, our data suggest that enhancement of cortical SSEPs is a result of action of etomidate on the primary sensory cortex.