Effects of Propofol, Etomidate, Midazolam, and Fentanyl on Motor Evoked Responses to Transcranial Electrical or Magnetic Stimulation in Humans

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The effects of propofol, etomidate, midazolam, and fentanyl on motor evoked responses to transcranial stimulation (tc-MERs) were studied in five healthy human volunteers. Each subject, in four separate sessions, received intravenous bolus doses of propofol 2 mg·kg⁻¹, etomidate 0.3 mg·kg⁻¹, midazolam 0.05 mg·kg⁻¹, and fentanyl 3 μg·kg⁻¹. Electrical tc-MERs (tc-ΔMERs) were elicited by anodal stimuli of 500–700 V. Magnetic tc-MERs (tcmag-MERs) were elicited using a Cadwell MES-10 magnetic stimulator at maximum output. Compound muscle action potentials were recorded from the tibialis anterior muscle. Duplicate tc-MERs and tcmag-MERs were recorded before and up to 30 min after drug injection. Reproducible baseline tc-ΔMERs (amplitude 4.7 ± 0.3 SEM mV, latency 29.4 ± 0.35 ms) and tcmag-MERs (amplitude 3.7 ± 0.43 mV, latency 31.1 ± 0.39 ms) were obtained in all subjects. Pronounced depression of tc-MER amplitude to 44% of baseline values (P < 0.01) was observed 2 min after injection of propofol. Thirty minutes after injection of propofol, amplitude depression to 44% of baseline values (P < 0.05) was still present, despite an apparent lack of sedation. Midazolam caused significant (P < 0.01) amplitude depression, e.g., tcmag-MER to 16% of baseline values 5 min after injection. Significant depression persisted throughout the 30-min study period. Fentanyl did not cause any statistically significant amplitude changes in this small population. Etomidate caused significant but transient depression of tc-ΔMER amplitude. However, there was considerable intersubject variability. Latency did not change significantly after any drug. The magnitude of drug-induced MER changes was similar for magnetic and electrical stimulation, although in two instances, at the peak of drug-induced depression, tcmag-MERs were absent when tc-ΔMERs were recordable. Since amplitude depression after etomidate was less pronounced and of shorter duration, etomidate may be preferable to propofol as an induction agent when tc-MER monitoring is indicated. Similarly, fentanyl may be preferable to midazolam as an intravenous supplement. (Key words: Anesthetics, intravenous: etomidate; fentanyl; propofol; midazolam. Magnetic stimulation. Monitoring, evoked potentials: motor evoked potentials. Transcranial stimulation.)

The occurrence of "false negatives" during intraoperative somatosensory evoked response (SSER) recording has provided a powerful incentive for the development of systems for monitoring conduction in descending motor pathways during spinal surgery. Several motor evoked response (MER) recording techniques, some of which involve invasive stimulation and/or recording procedures, have been investigated. An effective technique that is noninvasive and that entails stimulus and recording apparatus outside the surgical field would be valuable. Transcranial cortical stimulation with recording of motor responses from peripheral nerve or muscle (tc-MER) could meet these objectives.

Transcranial stimulation can be accomplished using either electrical or electromagnetic stimulators (fig. 1). Effective electrical stimulation requires a device that delivers a greater voltage output than can be achieved by typical SSER stimulators. Electromagnetic coil stimulators generate a strong (1.5-Tesla) transient magnetic field that induces a current in the underlying brain tissue. Transcranial stimulation results in an initial depolarization of either pyramidal cell neurons or their axons, followed by a descending volley in the pyramidal (and perhaps other) tracts. The efferent volley can be recorded from spinal cord using invasive techniques. After synaptic transmission to the α-motor neuron, the efferent activity can be recorded from peripheral nerve, and ultimately, after transmission across the neuromuscular junction, the resulting compound muscle action potential (CMAP) can be recorded from surface electrodes over the muscle.

Unfortunately, transcranial MERs (tc-MERs) appear to be extremely sensitive to depression by anesthetics.

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However, the available investigations do not provide information about all of the anesthetic agents commonly used in contemporary anesthesia. Furthermore, very few of the available data were derived in humans. In addition, although both electrical and magnetic transcranial stimuli have been used to elicit tc-MERs in vivo, there have been no attempts to determine whether the responses elicited by these two stimulus modalities differ in their sensitivity to degradation by anesthetic agents. The present investigation evaluated the effects of a single bolus dose of propofol, etomidate, midazolam, or fentanyl on tc-MERs to both electrical (tc-e-MERs) and magnetic stimulation (tc-mag-MERs) in human volunteers.

Materials and Methods

The study was approved by the local Human Subjects Committee. Five healthy physician members of the Department of Anesthesiology, four men and one woman, participated in the study. None had a history of epilepsy, psychiatric disorder, or the use any drugs known to lower seizure thresholds, e.g., tricyclic antidepressants and phenothiazines. The average age of the subjects was 33.4 yr (range 27–41 yr). The average height and weight were 171 ± 7 (SD) cm and 71 ± 6 kg respectively.

Each drug was studied at a separate session, with at least one week between sessions. Subjects fasted for 8 h before each session. Intravenous access was established with a 20-G cannula, and lactated Ringer’s solution was administered at a rate of 200 ml/h. Each subject breathed 50% oxygen by mask during the study period. The ECG, hemoglobin oxygen saturation by pulse oximetry (SpO₂), heart rate, and blood pressure were recorded. After completion of baseline tc-MER and tc-mag-MER recordings, each volunteer received propofol 2 mg·kg⁻¹, etomidate 0.8 mg·kg⁻¹, midazolam 0.05 mg·kg⁻¹, or fentanyl 3 μg·kg⁻¹ intravenously, injected over 30 s. When apnea lasting more than 30 s occurred, the subject’s lungs were ventilated by mask. The doses of propofol and etomidate were selected to represent those most commonly used for induction of anesthesia. Because these doses result in unconsciousness of less than 10 min duration, they not only permitted an assessment of the magnitude and duration of induction dose effects, but also provided an opportunity to examine effects of plasma concentrations spanning those that might be associated with maintenance of anesthesia with these agents. The doses of midazolam and fentanyl were chosen to reflect doses commonly used in clinical practice to supplement a general anesthetic technique. The doses used would normally be expected to produce mild sedation for the duration of the study period, but not unconsciousness.

Transcranial Electrical Stimulation

Electrical tc-MERs were elicited using a Digitimer D180-A electrical stimulator, specifically designed for transcranial electrical stimulation (Digitimer Ltd., Welwyn Garden City, U.K.). This stimulator delivers an electrical stimulus of up to 1,200 V, with a user-selectable time constant of 50 or 100 μs. Stimulus intensity is set with a rotary dial that is calibrated as percentage of maximum stimulator output. Stimulation was accomplished with conventional silver/silver chloride EEG disk electrodes (diameter 9 mm) attached to the scalp with collodion and filled with electrode jelly. The anode was placed at the vertex (C₃, International 10-20 System), and the cathode was placed 7 cm anteriorly. In accordance with the manufacturer’s recommendations, we did not reduce skin impedance at the stimulation sites, because the high stimulus voltage causes a breakdown of skin impedance. The 100-μs time constant was used in all subjects.

Transcranial Magnetic Stimulation

Transcranial magnetic stimulation was accomplished with a Cadwell MES-10 magnetic stimulator (Cadwell Laboratories, Kennewick, WA). This stimulator produces a transient, time-varying magnetic field (2 Tesla) by discharging a bank of capacitors through an isolated coil with a diameter of 9 cm. This time-varying magnetic field is capable of stimulating the cortex by generating a current in brain tissue below the coil. Stimulus intensity is set with
a rotary dial that is calibrated as a percentage of maximal output. The vertex electrode (used for tc-MER stimulation) was used as a "landmark" to ensure constancy of coil position. The coil was held firmly against the scalp with the vertex electrode at a constant location adjacent to the inner rim of the coil. In order to minimize variation between subjects with respect to the number of stimuli delivered prior to drug administration, no attempts were made to determine an "optimal" position for either the electrical or magnetic stimulation by moving the coil or the electrodes over the scalp.

**Compound Muscle Action Potential Recording**

Gold disk EEG electrodes were placed in a belly-tendon fashion on the tibialis anterior muscle bilaterally. Electrode impedances were kept below 2 kΩ. The CMAP occurring in response to transcranial stimulation was recorded with a Nicolet Pathfinder Mega evoked potential system (Nicolet Biomedical Instruments, Madison, WI). The muscle signal was amplified as appropriate for the size of the CMAP signal and was filtered between 10 and 3000 Hz (−3-dB roll-off). Single sweeps of 100-ms duration were recorded in duplicate and stored on magnetic disk for later analysis. Each session began with determination of the threshold for a detectable CMAP in response to first magnetic and then electrical stimulus. Thereafter, electrical and magnetic stimulus intensity was increased in 10% increments until no further augmentation of CMAP amplitude was observed (i.e., until a supramaximal stimulus was achieved) or until 100% of stimulator output was reached. That stimulus level was used throughout the session. The subjects were instructed to relax in order to avoid facilitation of the motor response by voluntary muscle contraction. Duplicate tc-MERs and tc<sub>mag</sub>-MERs were recorded before and 1, 5, 7, 10, 15, 20, 25, and 30 min after drug injection. Since time constraints did not permit recording and disk storage of both tc-MERs and tc<sub>mag</sub>-MERs at 1-min intervals, only tc-MERs were recorded at 2, 3, and 4 min after injection. The time to the onset of the response (latency) and the maximum peak-to-peak amplitude were measured off-line from the averaged waveform derived from each set of duplicate responses. Responses from the left and right tibialis anterior muscle were analyzed separately, but only results from the muscle that gave the larger baseline CMAP amplitude are reported.

**Statistical Analysis**

Tc-MER latency and amplitude data were analyzed by repeated-measures analysis of variance. Data are presented as mean ± SEM. Amplitude values were log-transformed to make the contribution of each subgroup to the total variance more uniform. Differences between baseline and subsequent timepoints were compared using t tests with Bonferroni corrections for multiple comparisons. A P value of less than 0.05 was considered significant.

**Results**

No significant changes in heart rate or SpO₂ occurred after administration of any of the agents. Mean arterial blood pressure decreased from 93 ± 3.7 to 81 ± 5.3 mmHg 5 min after administration of propofol (P < 0.05). Each subject received a total of 200 electrical stimuli and 170 magnetic stimuli during the four sessions. In a period of 6 months after participating in the study, none of the subjects has experienced any side effects that could be related to the use of transcranial stimulation.

Prior to drug administration, the threshold for a recordable anterior tibial muscle CMAP after transcranial electrical stimulation using the 100-μs time constant was 30 ± 3% of maximum output (± 360 ± 36 V). Supramaximal responses to electrical stimulation were obtained in all subjects at 46 ± 3% of maximum output (range 25–55%). The threshold for the recording of an anterior tibial muscle CMAP after transcranial magnetic stimulation was 66 ± 4% of maximum MES-10 output. Supramaximal responses after magnetic transcranial stimulation were obtained only in the woman volunteer (at 80% of maximum output). In the other four volunteers, the amplitude of the response increased when stimulus intensity was increased from 90 to 100% of maximum output, suggesting that a 100% output of the magnetic stimulator the motor cortex was probably not supramaximally stimulated.

Reproducible baseline tc-MERs (amplitude 4.7 ± 0.43 mV, latency 29.4 ± 0.35 ms) and tc<sub>mag</sub>-MERs (amplitude 3.7 ± 0.45 mV, latency 31.1 ± 0.39 ms) were recorded in each subject at each session. In each subject there was good concordance between baseline responses recorded at the four sessions (coefficients of variation between 15 and 25%). The average difference between left and right CMAPs was 35% of the mean value of the two responses. In individual volunteers the largest baseline response was usually found on the same side at each session. Responses recorded after transcranial electrical stimulation were larger than those recorded after magnetic stimulation (P < 0.001). Also, baseline latencies were significantly longer by 1.7 ± 0.25 ms with magnetic stimulation (P < 0.001). Figure 2 shows individual tc-MER waveform before and 2, 5, 10, and 30 min after injection of propofol, midazolam, etomidate, and fentanyl in one subject. Figure 3 presents the time course of tc-MER and tc<sub>mag</sub>-MER amplitude changes after each of the four drugs. In table 1, absolute values for $\text{tc}_e$-MER and tc<sub>mag</sub>-MER amplitudes are provided.
FIG. 2. Motor evoked response waveforms recorded from tibialis anterior muscle to transcranial electrical stimulation after injection of propofol 2 mg·kg⁻¹, etomidate 0.3 mg·kg⁻¹, midazolam 0.05 mg·kg⁻¹, or fentanyl 5 μg·kg⁻¹ in one subject. Duplicate waveforms have been superimposed to demonstrate reproducibility.

**Propofol**

All subjects lost consciousness within 30 s after completion of the injection of propofol 2 mg·kg⁻¹. Assisted ventilation was necessary in one subject for 6 min. Subjects regained consciousness between 4 and 7 min after injection. Ten minutes after administration of propofol all subjects were alert. Propofol caused significant depression of both tc-MER and tc_mag-MER amplitude (P < 0.01), which persisted throughout the study period. Maximum tc-MER amplitude depression, to 2.2 ± 0.9% of baseline, occurred 2 min after injection. Thirty minutes after injection, tc-MER and tc_mag-MER amplitudes remained significantly (P < 0.05) depressed, at 44 ± 23 and 44 ± 18% of baseline values, respectively. No significant changes in latency were observed after propofol.

**Midazolam**

Midazolam 0.05 mg·kg⁻¹ produced subjective and objective signs of sedation that persisted throughout the study period in all subjects. None of the subjects lost consciousness or required assisted ventilation. Sustained depression of tc-MER amplitude (P < 0.01) was observed after midazolam. Maximum depression of tc-MER and tc_mag-MER amplitude occurred 5 min after injection, at which time tc-MER and tc_mag-MER amplitude were 23 ± 9% and 16 ± 6% of baseline values respectively. Thirty minutes after injection of midazolam tc-MER amplitude was 40 ± 22% of baseline and tc_mag-MER amplitude was 28 ± 19%. No changes in latency occurred after midazolam.

**Etomidate**

Etomidate 0.3 mg·kg⁻¹ produced unconsciousness of slightly longer duration than propofol (range 5–7 min).

No subject required ventilation. All subjects exhibited myoclonus during the first minutes after injection. The myoclonus ranged from fine movements in the fingers to tonic–clonic limb movements. The changes in tc-MER were extremely variable from subject to subject. In the subject who showed pronounced myoclonic movements, amplitudes increased (tc-MER to 239% and tc_mag-MER to 243% of baseline at 5 min). In the other subjects there were variable degrees of amplitude depression. A significant decrease in tc-MER amplitude (P < 0.05) was only observed 2 min after injection of etomidate. In the five subjects, the maximum tc-MER amplitude depression ranged from 57 to 7% of baseline, and tc_mag-MER depression ranged from 72 to 1.6% of baseline. No changes in latency were observed after etomidate.

**Fentanyl**

Fentanyl 5 μg·kg⁻¹ produced mild sedation for the duration of the study period in all subjects. There was a trend toward depression of tc_mag-MER amplitude (56% of baseline) 15 min after injection of fentanyl, but this was not statistically significant in this small population. There were no changes in either tc-MER amplitude or latency.

There was a good correlation between the amplitude of the CMAP responses elicited by the two modes of transcranial stimulation (r = 0.89, P < 0.001). Amplitudes after magnetic stimulation were approximately 70% of those observed after electrical stimulation. There was no statistically significant difference in the relative depression of tc_mag-MER and tc-MER amplitude after propofol or midazolam. However, at the peak of propofol-induced amplitude depression, tc_mag-MERs were absent in two subjects when tc_MERs were present.
Discussion

The results of the present study indicate that substantial depression of tc-MER amplitude occurs after an induction dose of propofol or a sedative dose of midazolam, whereas an induction dose of etomidate and a sedative dose of fentanyl cause smaller and less prolonged decreases in amplitude. None of the drugs studied had any significant effect on tc-MER onset latencies, even when amplitude was decreased below 10% of baseline values.

The mechanism by which anesthetic drugs produce depression of tc-MER amplitude is unknown. The potential loci for the effects that were observed include the motor cortex, the axons of corticospinal tract neurons, the spinal cord at the level of the α-motor neurons, the peripheral nerve, and the myoneural junction. Effects related to the latter two are unlikely to have contributed. Anesthetic agents have been shown to have little effect on peripheral nerve conduction. With respect to the myoneural junction, even volatile anesthetics, which are known to potentiate neuromuscular blockade to a greater extent than intravenous anesthetic agents, exert a direct effect on twitch height only in concentrations above 1.5 MAC. Corticospinal neurons, the α-motor neurons in the spinal cord and their respective interneuronal systems, are more likely loci of action for the effects that we have observed. However, the design of our study does not allow us to discriminate between effects at cortical and spinal levels.

The marked decreases in tc-MER amplitude that we observed after propofol are similar to those observed in monkeys after thiamylal, and comparable tc\textsubscript{mag-MER}

![Graphs showing the effect of different anesthetics on tc-MER amplitude](https://example.com/graphs.png)

**Fig. 3.** Amplitudes (millivolts, mean ± SEM) of motor evoked responses to transcranial electrical or magnetic stimulation versus time after injection of propofol 2 mg·kg\textsuperscript{-1}, etomidate 0.3 mg·kg\textsuperscript{-1}, midazolam 0.05 mg·kg\textsuperscript{-1}, or fentanyl 3 μg·kg\textsuperscript{-1}. *p < 0.05; **p < 0.01.
amplitude depression was observed in human volunteers during a continuous infusion of midazolam 0.3 mg·kg⁻¹·h.¹³ The post-propofol amplitude suppression was prolonged even though all of our subjects were clinically completely awake well before the end of the recording period. This marked disparity between the electrophysiologic effects and the apparent effects on consciousness is unexplained. However it is consistent with an important site of action other than cerebral cortex.

Two techniques are currently available for noninvasive transcranial stimulation of the motor cortex—magnetic and electrical. Both methods have been compared extensively in awake human subjects.¹⁹-­²⁰ Since electrical stimulation is moderately painful, magnetic stimulation has been used more commonly in investigations of tc-MER in awake patients. With both stimulus techniques, stimulation is believed to occur at the level of the cerebral cortex. However, the precise site of activation probably differs. In numerous investigations, the latency of the CMAP response from hand muscles has been shown to be approximately 2 ms longer after magnetic stimulation than after electrical stimulation.²¹-²⁴ It is believed that transcranial electrical stimulation directly activates corticospinal tract neurons. This results in a descending volley in the corticospinal tract consisting of an initial direct or “D”-wave, which is followed by multiple indirect “I”-waves. The latter are believed to occur as a result of activation of excitatory cortical interneurons that cause additional firing of the corticospinal tract neurons. After electrical stimulation, the first components of the CMAP are initiated by the arrival of the D-wave. In contrast, magnetic stimulation appears to produce a descending volley consisting of “I”-waves only,²¹ and as a result the onset of the CMAP is somewhat delayed. The results of the present investigation are consistent with these theories and previous studies in that, whereas the amplitudes and general configuration of the tibialis anterior CMAPs were comparable, the latency to the onset was approximately 1.7 ms longer after magnetic stimulation.

It has been suggested, because initiation of the efferent corticospinal volley after magnetic stimulation probably involves a synaptic event, that tc_mer-MERs might be more susceptible to anesthetic-induced amplitude depression.¹² The two modes of transcranial stimulation have not been compared previously in the presence of anesthetic drugs. The present data, superficially examined, might suggest that, with the anesthetic agents, instruments, and monitoring parameters used, tc_e-MERs were somewhat more “robust” than tc_mer-MERs. However, this investigation suffers from a significant limitation with respect to this type of comparison. With the stimulators used it was possible to achieve a supramaximal (in terms of CMAP response amplitude) level of stimulus for electrical but not for magnetic stimulation. Consistent with this difference is the observation that baseline responses after magnetic stimulation were of lesser amplitude than after electrical stimulation. The question of the relative “robustness” of tc_mer-MERs and tc_e-MERs will require further investiga-
tion, ideally conducted with techniques that will permit the use of supramaximal stimuli for both stimulus modalities.

The tc-MERs recorded in this investigation were duplicate responses to single stimuli. It is possible that a signal averaging approach would have resulted in recordable responses in those few instances in which the tc-MER was abolished. However, this approach would substantially increase the total number of electrical or magnetic stimuli applied, thereby increasing the net charge delivered to the brain. The safety record of transcranial stimulation, with respect to evoking seizure activity or to causing long-term psychological sequelae is promising. However, the experience to date has involved stimuli applied at widely spaced intervals (10 s or longer). It seems imprudent to avoid multiple stimuli at short intervals in humans pending a more detailed examination in animals of the safety of this approach.

The present study together with the results of previous investigations indicate that the anesthetic constraints relevant to the recording of tc-MERs are different from those that apply to the recording of SSERs. For instance, SSERs are well preserved after administration of both propofol and benzodiazepines. However, the present data indicate that sustained reduction of tc-MER amplitude occurs after a single dose of propofol of 2 mg·kg⁻¹. It is likely that very high blood concentrations are achieved in the initial minutes after administration of an induction dose of propofol. Accordingly, the results obtained within the first few minutes after propofol administration should not be used to draw inferences about the likely effects of propofol in the doses used to maintain anesthesia. However, our consistent observation of sustained amplitude depression after our subjects were awake and fully conversant suggests that propofol is also a powerful depressant of tc-MER amplitude at plasma concentrations needed for total intravenous anesthesia. In contrast, etomidate appears to be compatible with the recording of both SSERs and tc-MERs. Etomidate is, in fact, unique among the anesthetic drugs in that it causes an increase in SSER amplitude. This effect is believed to be mediated at the level of the cerebral cortex, and it is therefore possible that the augmentation of SSERs and the apparent preservation of tc-MERs are in some way related physiologically.

All of the clinical studies of tc-MER monitoring published to date have used a nitrous oxide/opioid anesthetic technique, and our data suggest that the use of fentanyl should be consistent with recordable tc-MERs. Nitrous oxide, however, is known to depress tc-MER CMAP amplitude. But, some addition to an opioid is usually necessary, and it appears that nitrous oxide is a less potent suppressant of tc-MER amplitude than equi-MAC concentrations of the volatile agents. In a clinical investigation, it was observed that isoflurane 0.2–0.3% abolished tc-MERs during nitrous oxide/opioid anesthesia in humans. It has also been shown that halothane and isoflurane produce significant depression of CMAP amplitude after direct electrical stimulation of the motor cortex in rats. Accordingly, although nitrous oxide causes significant attenuation of the tc-MER it may nonetheless be preferable to a volatile agent if an inhaled anesthetic is required. In our own clinical practice we have adopted an anesthetic regimen that uses etomidate as the induction agent and maintains anesthesia with nitrous oxide and sufentanil in a bolus-plus-infusion regimen.

In summary, the present investigation indicates that MERs to transcranial electric and magnetic stimulation are well preserved after an induction dose of etomidate or a sedative dose of fentanyl, whereas substantial depression of amplitude occurs after an induction dose of propofol or a sedative dose of midazolam. The pattern of change in tc-MERs to magnetic and electric stimulation was in general quite similar, although the data suggest that, with the stimulus and recording parameters used in the present investigation, magnetic motor responses may be slightly more vulnerable to degradation by anesthetic agents.

References


