The Effects of Volatile Anesthetics on Intraoperative Monitoring of Myogenic Motor-Evoked Potentials to Transcranial Electrical Stimulation and on Partial Neuromuscular Blockade During Propofol/Fentanyl/Nitrous Oxide Anesthesia in Humans

[Clinical Investigation]

Sekimoto, Kenichi MD; Nishikawa, Koichi MD, PhD; Ishizeki, Junko MD; Kubo, Kazuhiro MD; Saito, Shigeru MD, PhD; Goto, Fumio MD, PhD
Department of Anesthesiology, Gunma University Graduate School of Medicine, Showa-machi, Maebashi City, Japan
Supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture of Japan to K.N. (17390425 and 17659483).
Reprints: Koichi Nishikawa, Department of Anesthesiology, Gunma University Graduate School of Medicine, 3-39-22 Showa-machi, Maebashi City 3718511, Japan (e-mail: nishikaw@med.gunma-u.ac.jp).
Received for publication August 19, 2005; revised November 10, 2005; accepted November 10, 2005

Outline

Abstract

METHODS

Patients

General Anesthesia and Study Protocol

MEP Monitor and Recording

Data Analysis and Statistics

RESULTS

Effects of Volatile Anesthetics on Hemodynamic Parameters

Effects of Volatile Anesthetics on NMB
Effects of Volatile Anesthetics on MEPs
Recovery and Postoperative Complications

DISCUSSION

Effects of Volatile Anesthetics on NMB During Propofol Anesthesia

Volatile Anesthetics and MEP Monitoring

Side Effects

CONCLUSIONS

REFERENCES

Graphics

Table 1
Table 2
Figure 1
Figure 2
Figure 3
Figure 4

Abstract

The aim of the present study was to compare the influence of volatile anesthetics on transcranial motor-evoked potentials (tcMEP) in humans anesthetized with propofol/fentanyl/nitrous oxide and on partial neuromuscular blockade (NMB). The authors studied 35 ASA I and II patients who were undergoing elective craniotomy and brain tumor resection. The patients were randomized to one of three groups to receive halothane (HAL), isoflurane (ISO), or sevoflurane (SEV). Anesthetic depth was initially adjusted using the bispectral index to 40+/5, and NMB was adjusted to 40%-50% of one twitch of train of four (T1) after recovery from intubation. MEPs with train of five square-wave pulses were elicited using screw electrodes placed in the skull over C3-C4. After craniotomy, the inhalational agent was introduced at 0.5 MAC and then 1.0 MAC (20 minutes each), and the effects on MEPs, NMB, and hemodynamic variables were studied. A decrease in BIS and systolic blood pressure was observed with all agents. Both SEV and ISO at 1.0 MAC significantly decreased train-of-four ratio from 38.4+/18.1 at control to 19.0+/9.7 and from 35.3+/12.4 to 26.1+/13.7, respectively (P
Monitoring of transcranial motor-evoked potentials (tcMEPs) provides useful information about the functional integrity of descending motor pathways during invasive manipulation of the central nervous system. Thus, MEP monitoring is widely used during neurosurgery, spine surgery, and thoracoabdominal aorta replacement. However, experimental and clinical studies have shown that MEPs are suppressed by most anesthetic agents such as midazolam, propofol, and volatile anesthetics in a dose-dependent manner. Especially, MEPs are known to be sensitive to volatile anesthetics. Intravenous anesthetics are preferentially used during MEP monitoring. Although recent advances in techniques using multipulse transcranial stimulation have broadened the spectrum of anesthetics that can be used during MEP monitoring, the choice and maintenance of anesthesia are still of great interest for anesthesiologists.

Myogenic MEPs are elicited by transcranial stimulation over the motor cortex and recorded by electrodes placed in muscles that correspond to the neural pathway at risk during the surgery. Therefore, intraoperative management of neuromuscular blockade (NMB) is also critical to myogenic MEP recording, in which some blockade should be useful for maintenance of anesthesia but excessive blockade may eliminate the responses. Although ideal anesthetic regimens during MEP monitoring may vary depending on the type of surgery, there is still controversy about the degree of NMB. This emphasizes the need for evaluation of the effects of volatile anesthetic inhalation during propofol-based anesthesia on NMB.

This study was therefore conducted to compare the effects of halothane, isoflurane, and sevoflurane on monitoring of tcMEPs in humans anesthetized with propofol/fentanyl/nitrous oxide anesthesia and on NMB produced by a continuous infusion of vecuronium.

METHODS

Patients

After obtaining approval from the institutional ethical committee and informed consent, 36 patients (ASA status I or II), in whom elective craniotomies were performed for brain tumor resection, were enrolled in this study. Because all patients were considered to be at relatively high risk for postoperative neurologic deterioration, MEP was used with approval by our institutional review board. Patients with a history of stroke, myasthenia gravis, and other neuromuscular disorders were excluded from the study. No premedication was given before anesthesia. Patients were randomly allocated into one of three groups to receive halothane (HAL), isoflurane (ISO), and sevoflurane (SEV). In the operating room, two 18-gauge cannulas were inserted into a large forearm vein: one for drug administration and the other for fluid or blood infusion. Lactated Ringer solutions were infused at a rate of 5-10 mL/kg/h. Electrocardiogram, arterial blood pressure, heart rate, SpO2, end-tidal CO2 concentration, end-tidal anesthetic concentration, and rectal body temperature were monitored.
using anesthesia monitoring system (Hewlett Packard Japan, Tokyo, Japan). A radial artery catheter was inserted for monitoring of arterial blood pressure. Muscle relaxation was monitored with a Relaxograph (Datex, Finland) from the adductor pollicis brevis muscle. Control data of train of four (TOF) were obtained before a neuromuscular blocking drug was given. The bispectral index (BIS) was also monitored continuously using the Aspect EEG monitor (A-2000; Aspect Medical Systems, Newton, MA). Following alcohol cleaning, disposable BIS sensor electrodes (BIS sensor plus; Aspect Medical Systems) were applied to the forehead of patients to record the preinduction value. Impedance of the electrodes was confirmed to be less than 500 [OMEGA].

**General Anesthesia and Study Protocol**

Routine physiologic monitoring was started, and baseline values were recorded while the patient breathed 100% oxygen. After breathing 100% oxygen for at least 3 minutes through a facemask, general anesthesia was induced with a single dose of propofol (2 mg/kg) and fentanyl (1-2 [mu]g/kg). To facilitate tracheal intubation, vecuronium bromide (0.1 mg/kg) was injected immediately after loss of consciousness (eyelash reflex) occurred. After intubation, a bite block was used to prevent tooth and tongue damage when the jaws were brought together forcefully by high frequency transcranial electrical stimulation. General anesthesia was initially adjusted and maintained with oxygen (33%), nitrous oxide (67%), and propofol infusion using BIS within the range of 40+/-5. Ventilation was controlled to maintain end-tidal PaCO2 at approximately 28-33 mm Hg. Fentanyl (4 [mu]g/kg) was injected in bolus doses before the operation but was avoided during the study period to minimize its hemodynamic effects. NMB with vecuronium was also adjusted using a Datex Relaxograph to provide 40%-50% of one twitch of TOF (T1) after recovery from intubation. The muscle being recorded for NMB was also kept warm and maintained within +/-1[degrees]C by using a warming blanket. In some patients, an intrathecal catheter was placed in the lumbar intervertebral space, and spinal drainage was continued to maintain intrathecal pressure at less than 10 mm Hg.

When anesthetic depth and NMB were stable after craniotomy, the inhalational anesthetic was then introduced at 0.5 MAC and then 1.0 MAC (20 minutes each) with at least 1-hour interval: 0.35% and 0.7% for HAL, 0.6% and 1.2% for ISO, and 0.9% and 1.8% for SEV. Different anesthetic was not administered in the same patient. The effects of volatile agent on MEPs, NMB, and hemodynamic variables were recorded every 5 minutes. Neither vasopressor nor vasodilator was used during the study period to avoid its effects on neuromuscular monitoring. However, when systolic blood pressure was increased over 140 mm Hg or decreased less than 80 mm Hg during the study period, nicardipine or phenylephrine was used to treat hemodynamic changes, and the case was excluded from further analysis.

**MEP Monitor and Recording**
Myogenic MEPs to anodal stimulation (C3-C4) were elicited with train-of-five square-wave pulses (duration 400 microseconds, intensity

MEPs were elicited using metal screw electrodes placed in the outer table of the skull over the primary motor cortex. Cases in which the location of craniotomy overlapped stimulation sites were avoided. The electrical responses were recorded using electromyography from the adductor pollicis brevis and tibialis anterior muscles, in which paired needle electrodes (2 cm apart) were placed subcutaneously. The threshold current intensity needed to evoke MEPs was monitored throughout the operation. The stimulus intensity was adjusted to supramaximal and kept at the same level during the study. In usual cases, stimulation intensities over 100 mA were used. At least two recordings were done at each level. The signals were sampled at 1 kHz and digitized with an A/D converter and displayed on a standard PC screen. The amplitude was measured as the voltage from the most negative component to the most positive of the evoked activity.

Data Analysis and Statistics

Sample size was estimated using an expected difference of the amplitude of MEPs at 1.0 MAC for a power of 0.8 and [alpha]=0.05 (sample power 2.0; SPSS, Chicago, IL). All data are expressed as means+/-SD. Statistical analysis was performed using StatMate version III for Windows (ATMS Co., Tokyo, Japan). Statistical difference was assessed by one-factor repeated measures analysis of variance followed by the Tukey test as a post hoc test for each group. P

RESULTS

The patients' characteristics are shown in Table 1. Hypotension less than 80 mm Hg was observed after 20 minutes application of HAL at 1.0 MAC in two patients, who was successfully treated with phenylephrine according to study protocols. Therefore, two patients in the HAL group were excluded from analysis, and the data from 34 patients were analyzed.

TABLE 1. Demographic Data of the Patients

Data are expressed as means+/-SD. There was no significant difference in age, body weight, or dose of propofol among groups.
No significant differences were observed in age, weight, and other parameters among three groups. The baseline, nonmedicated BIS values of the three groups were around 97-98. The mean infusion rate of propofol before the administration of the study drug was 6.5 +/- 1.3 mg/kg/h (n=34; Table 1), and no significant difference in the infusion rate was observed among the three groups. The infusion rate of vecuronium was also similar among three groups (Table 1).

Effects of Volatile Anesthetics on Hemodynamic Parameters

Systolic blood pressure was significantly decreased after the introduction of 1 MAC volatile anesthetics at 5, 10, 15, and 20 minutes without affecting heart rate during volatile agent application (Table 2). All volatile anesthetics significantly decreased the BIS score, but burst suppression was not observed during the application (Table 2).

TABLE 2. Changes in Parameters Produced by the Drug Application (1.0 MAC) During Propofol-Based Anesthesia

Data are presented as means+/−SD.*PPP

Effects of Volatile Anesthetics on NMB

Figure 1 shows representative recordings of the effects of volatile anesthetics on partial NMB. There was no significant difference in TOF ratio between agents at control. Figure 2 summarizes the effects of three volatile anesthetics at 1.0 MAC on TOF ratio. SEV (1.8%) significantly decreased TOF ratio from 38.4+/−18.1 at control to 19.0+/−9.7 at 20 minutes after application (PPP=0.225). HAL (0.7%) decreased TOF ratio from 37.3+/−17.4 at control to 28.5+/−16.6, but this change did not reach a statistically significant level (P=0.4, n=10). The degree of depression produced by HAL was significantly smaller than that of SEV (P

FIGURE 1. A sample trace of the effects of volatile anesthetics on NMB. Vecuronium bromide (0.1 mg/kg) was injected to facilitate tracheal intubation (arrow); after partial recovery of NMB was confirmed on the monitor (T1 >50%), continuous infusion of vecuronium was started and titrated to provide 40%-50% of
one twitch of TOF (T1) delivered to the ulnar nerve at the wrist. Gray bars indicate T1; black bars indicate TOF ratio. This is a trace to show the effects of multiple anesthetics on NMB, although no patient had two different inhalation agents.

---

FIGURE 2. Summary of the effects of volatile anesthetics at 1.0 MAC on TOF ratio during propofol anesthesia. After baseline data were obtained, volatile inhalation was started. SEV and ISO produced a significant decrease in TOF ratio, whereas HAL had no effect on the amplitude. Data are expressed as means+/-SD. *PPPP

---

Effects of Volatile Anesthetics on MEPs

Figure 3 shows examples of MEP waveforms to train-of-five square-wave pulses and the effects of SEV and ISO. Figure 4 summarizes the effects of volatile anesthetics on the amplitude of MEPs. All volatile anesthetics significantly depressed the amplitude of MEPs (21.2%+/-14.4%, 20.5%+/-23.4%, 17.7%+/-30.46% of control at 1.0 MAC; PP

---

FIGURE 3. Sample traces of volatile anesthetics on MEPs during propofol/fentanyl/nitrous oxide anesthesia. Volatile anesthetics depressed the amplitude of MEPs. This is a trace to show the effects of multiple anesthetics on MEPs, although no patient had two different inhalation agents.

---
Recovery and Postoperative Complications

No significant change in recovery time, the time from propofol discontinuation to extubation, was noted among three groups: HAL 10.9+/−8.6 minutes, ISO 17.0+/−7.5 minutes, and SEV 11.4+/−6.3 minutes (P>0.05). No major complication was observed after general anesthesia.

DISCUSSION

The results in the present study are summarized as follows: SEV and ISO produced a significant decrease in TOF ratio, whereas HAL had no effect on TOF ratio; the amplitudes of tcMEPs were significantly reduced by all agents at 1.0 MAC, with the effect being less for HAL at 0.5 MAC. To the best of our knowledge, this is the first study to compare the influence of volatile anesthetics on MEP recordings and on partial NMB during propofol-based anesthesia.

Effects of Volatile Anesthetics on NMB During Propofol Anesthesia

Myogenic MEPs are affected by the level of NMB. Some blockade should be useful for maintenance of anesthesia to provide stable surgical field, but excessive blockade may eliminate the MEP responses. The degree of the ideal level of NMB is still controversial. For example, Kalkman et al 17 have recommended using NMB to maintain one or two mechanical responses to TOF stimulation of the ulnar nerve. Adams et al 18 have demonstrated that the intraoperative monitoring of myogenic MEPs was feasible under conditions of controlled NMB to maintain T1 at 10% of the baseline value. On the other hand, van Dongen et al 19 have reported that six-pulse (rather than two-pulse) transcranial electrical stimulation during a stable anesthetic state and a stable NMB, aimed at 45%-55% (rather than 5-15%) of baseline, provide reliable and recordable muscle responses sufficiently robust for spinal cord monitoring in aortic surgery.

We found that the degree of MEP depression produced by HAL at 0.5 MAC was significantly smaller than those of ISO or SEV. These data suggest that HAL at 0.5 MAC may be useful for MEP monitoring during propofol-based neuroanesthesia. From our data, the reduction of T1 and TOF ratio would certainly be expected to reduce MEP amplitude; however, these two parameters were not reduced by volatile agents in parallel. These data suggest that tcMEPs may be affected by not only
the level of NMB but also the effects of volatile agents in combination with propofol on nerve conduction or synaptic transmission in descending motor pathways.

Volatile Anesthetics and MEP Monitoring

A number of previous studies have demonstrated that volatile anesthetics depress the amplitude of MEPs in a dose-dependent manner. For example, the addition of 1% ISO with nitrous oxide in oxygen and with narcotics abolished the single pulse-induced MEPs in five of eight patients.6 Similar results were also found in animal experiments such as rats and rabbits.12 Taken together, during the monitoring of myogenic MEPs, the administration of volatile anesthetics should be limited to low concentrations. To minimize anesthetic-induced depression of myogenic MEPs, combined use of anesthetic agents (so-called balanced anesthesia) or total intravenous anesthesia has been recommended for improvement of intraoperative MEPs monitoring. For example, Taniguchi et al 20 compared the influence of continuous infusion of intravenous anesthetics agents on transcranial magnetic MEPs and found that etomidate and methohexital were relatively detrimental anesthetic agents for monitoring compared with propofol and thiopental.

We agree that intravenous anesthetics such as propofol, fentanyl, and ketamine may have some advantages for MEP monitoring; however, our data indicate that 20-minute inhalation of volatile anesthetics has depressed the amplitude of MEPs to approximately 20% of control, but MEP monitoring were still possible in our recording conditions. Especially, the effect of 0.5 MAC HAL on MEPs was smaller than those of other agents. Therefore, we think that low concentrations of volatile anesthetic such as halothane can be used during propofol/fentanyl anesthesia. Progress in stimulation technique may improve MEP recording. First, myogenic MEPs were elicited with train-of-five square-wave pulses in our study to overcome anesthetic-induced depression of MEPs. Second, transcranial electrical stimulation through screw electrodes was used to improve MEP responses.16 MEPs were elicited using metal screw electrodes placed in the outer table of the skull over the primary motor cortex. Passing current through the screw electrodes may stimulate the motor cortex more effectively than conventional methods. However, it should be noted that our results may not apply to MEP recording in which electrodes are placed outside the bone. Therefore, this study does not provide the evidence that all patients having MEP monitoring should be able to have low-dose inhalational agent during propofol-based anesthesia.

Side Effects

One side effect of application of volatile anesthetics during propofol anesthesia is hypotension. Generally, a mean arterial pressure less than 60 mm Hg impairs cerebral autoregulation and cerebral blood flow; therefore, hypotension during SEV application may induce reduced cerebral perfusion.
pressure. Judging from the BIS data, coadministration of anesthetics produced deep anesthesia (Table 2); in fact, the BIS score were at the 20 s, but burst suppression was not observed even in this condition. Therefore, we think that transient (20-minute) application of a volatile anesthetic during propofol anesthesia is within a reasonable range in terms of anesthetic depth.

CONCLUSIONS

Our data provide evidence that halothane has less suppressive effects on TOF ratio than ISO and SEV and that HAL at 0.5 MAC during propofol-based anesthesia can be used for the MEP monitoring.

REFERENCES


Key Words: motor-evoked potentials; volatile anesthetics; neuromuscular blockade; muscle relaxant

---------------------------------------------
Accession Number: 00008506-200604000-00003