Total intravenous anesthesia for intraoperative monitoring of the motor pathways: an integral view combining clinical and experimental data

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Object. Monitoring of descending corticospinal pathways by using motor evoked potentials (MEPs) has proven to be useful in preventing permanent neurological deficits during cranial and spinal procedures. Difficulties in interpretation of intraoperative changes in potentials may largely be attributed to the effects of anesthesia. Development of suitable intravenous anesthesia protocols specifically tailored for MEP monitoring, including plasma level target-controlled infusion (TCI), requires precise knowledge of the specific neurophysiological properties of the various agents.

Methods. The effects of alfentanil, sufentanil, fentanyl, remifentanil, thiopental, midazolam, etomidate, ketamine, and propofol on neurogenic and myogenic MEPs were evaluated in an integral study combining clinical data obtained in 40 patients and experimental investigations conducted in 140 animals. The dose-dependent modulation of MEPs after electrical and magnetoelectrical stimulation of the motor cortex was recorded from peripheral muscles and the spinal cord.

The results were as follows: opioids, propofol, and thiopental suppressed myogenic, but not neurogenic MEPs in a dose-dependent fashion; remifentanil exerted the least suppressive effects. Etomidate and midazolam did not suppress myogenic MEP, even at plasma concentrations sufficient for anesthesia. Ketamine induced moderate reduction of compound muscle action potential amplitudes only at high doses. Remifentanil and propofol administered via TCI systems allowed recording of myogenic potentials within a defined target plasma concentration range.

Conclusions. Development of standardized total intravenous anesthesia/TCI protocols by using anesthetic agents such as propofol, remifentanil, ketamine, and midazolam, which have favorable pharmacokinetic and neurophysiological properties, will enhance the quality of intraoperative MEPs and promote the use of MEP monitoring as a useful tool to reduce surgery-related morbidity.

Key Words • anesthesia • neurophysiology • motor evoked potential • target-controlled infusion • rabbit

INTRAOPERATIVE recording of MEPs has been progressively integrated into the electrophysiological monitoring of neurosurgical patients. Various recording methods have been investigated with respect to different stimulation modalities. The main goal has been to improve the assessment of different components of the motor system and to enhance both the sensitivity and specificity of MEP findings. Reliable interpretation of myogenic potentials elicited by transcranial electric or magnetoelectric stimulation of the motor cortex and recorded from extremity muscles is compromised, however, by a number of factors, mainly by the influence of general anesthesia. In earlier investigations it has been shown that volatile anesthetic agents induce marked suppression of both neurogenic and myogenic potentials at alveolar concentrations commonly used in neuroanesthesia. Therefore, numerous studies have been undertaken to quantify the effects of various intravenous anesthetic agents on MEPs. Nevertheless, a systematic approach that addresses the choice of the most appropriate anesthetic protocol, depending on individual requirements for both anesthesia and electrophysiological monitoring, has been lacking. Therefore, difficulties in the interpretation of intraoperative MEP findings remain; these are caused by the complex effects of intravenous anesthetics on these potentials, including changes in neuronal excitability, modulation of electrical impulse transmission, and neuromuscular transmission, as well as systemic side effects (reduction of MABP and reduction of muscle blood flow). This study was designed to elaborate the specific properties of different intravenously administered anesthetic drugs currently used for neuroanesthesia with regard to their impact on myogenic and neurogenic MEPs elicited by both electrical and magnetoelectric stimulation of the motor cortex. Special emphasis is placed on the effects of different stimulation paradigms, as well as the implications and new perspectives associated with the administration of intravenous anesthetic agents via TCI systems.

Abbreviations used in this paper: bw = body weight; CMAP = compound muscle action potential; DPS = double-pulse stimulation; EEG = electroencephalographic; ESCP = evoked spinal cord potential; MABP = mean arterial blood pressure; MEP = motor evoked potential; QPS = quadruple-pulse stimulation; SD = standard deviation; SPS = single-pulse stimulation; TCI = target-controlled infusion.
Materials and Methods

Experimental Investigations

The effects of alfentanil, sufentanil, fentanyl, remifentanil, thiopental, midazolam, etomidate, ketamine, and propofol on neurogenic responses (that is, ESCP) and myogenic MEPs were evaluated in 140 rabbits. All animal experiments were conducted in accordance with the Institutional Animal Care and Use Committee guidelines and approved by the governmental review board. The protocol has been described in detail elsewhere.8

Animal Preparation. After tracheostomy, the animals underwent ventilation with an O2–air mixture (60% O2/40% air) to maintain the PaO2 between 100 and 150 mm Hg and the SaO2 above 98%. Endtidal CO2 was kept between 35 and 45 mm Hg. The arterial PaO2, PaCO2, and pH were kept constant within their physiological range. The body temperature was maintained at 37°C, and the MABP measured in the lower aorta was maintained between 60 and 80 mm Hg. Central venous pressures recorded in the inferior vena cava were adjusted to between 2 and 6 mm Hg. Electrocardiographic data were recorded through needle electrodes placed in the lateral chest wall. Electroocortical activity was recorded through eight bilateral frontal- toparietal leads that were fixed on the skull by using miniature screw electrodes.

Electrode Implantation. The head of the animal was secured in a stereotactic frame, and a trephination exposing the left frontoparietal area was performed. Two silver ball stimulation electrodes were placed in the epidural space under the rostral and laterocaudal bone margins of the trephination. The left motor cortex was stimulated at the suprathreshold intensity (threshold intensity + 50%) by a constant voltage stimulator. The CMAPs (also referred to as myogenic potentials) were recorded from the upper- and lower-extremity muscles, whereas ESCPs (also known as neurogenic responses) were registered from the upper and lower thoracic spinal cord (Spirit Evoked Potential System; Nicolet Biomedical, Madison, WI).

Induction of Anesthesia. Anesthesia was induced with etomidate (0.5 mg/kg bw) and remifentanil (1 μg/kg bw/min), which were supplemented with cis-atracurium (Tracrium, Glaxo-Wellcome, Bad Oldesloe, Germany) during the surgical procedure. These agents were chosen because of their short elimination half-life. After placement of all temperature and recording electrodes, a state of anesthesia was maintained by continuous infusion of each anesthetic agent being investigated. This was done to establish stable baseline conditions, including reproducible baseline MEPs at all recording sites, thus precluding influences from the induction agents. Then, either the infusion rate or the bolus dose of each anesthetic agent being investigated was adjusted to establish distinct clinical and electrophysiological end points as follows: surgical anesthetic depth (defined as the lowering of heart rate and EEG response to an abdominal and plantar skin incision), and, if possible, extinction of myogenic responses recorded from various muscle groups in the extremities. The ratio of the drug quantity administered (or target plasma concentration) derived from these two end points may be considered to be a dosage window for the monitoring of myogenic MEPs.

Clinical Investigations

The TCI systems have been devised for plasma level–oriented application of short-acting intravenously administered anesthetic agents. These systems use a pharmacokinetic model based on the principal distribution compartments of the human body and the individual distribution and elimination constants of an intravenously administered anesthetic agent infused at a constant rate. Two short-acting anesthetic drugs currently used in neuroanesthesia (propofol and remifentanil), which offer favorable properties for total intravenous anesthesia, were administered at increasing target plasma concentrations by using computerized TCI systems.

| Patient Population. Forty patients (20 men and 20 women) who were about to undergo spinal surgery were enrolled in our study after informed consent. The study protocol was approved by the institutional ethics review board. The mean age of our patient population was 42 ± 8.3 years (mean ± SD). Preoperative neurological and electrophysiological assessments (electromyography and transcranial MEPs of the target muscles) were performed in each patient. Individuals with preexisting motor deficits were excluded from the study protocol. All patients received a 1-mg oral dose of flunitrazepam as premedication approximately 12 hours before surgery. No other sedatives or centrally acting agents were given before induction of anesthesia. The MABP (>70 mm Hg), blood SaO2 (>97%), and body temperature (37–37.5°C) were continuously assessed and kept constant. During the induction sequence for anesthesia, propofol and remifentanil target plasma concentrations were increased in a stepwise fashion from 0 to 6 μg/ml (propofol: 0, 1, 3, and 6 μg/ml) and 0 to 15 ng/ml (remifentanil: 0, 3, 9, and 15 ng/ml), respectively, to establish a dose–response relationship. No additional anesthetics or muscle relaxants were used until endotracheal intubation was performed (designating the end point of the individual study protocol in a given patient), to preclude undesired effects from substances other than the induction agent.

Recording of Potentials. The MEPs (also referred to as CMAPs) were recorded from the abductor pollicis brevis, abductor digiti minimi, and lower arm flexor muscles by using surface Ag/AgCl electrodes. Standard electrophysiological equipment was used to record the MEP. The high-pass filter was set to 30 Hz and the low-pass filter to 3 kHz; the notch filter was deactivated. We used a multipulse magnetic stimulation capable of delivering repetitive stimulative stimuli at frequencies ranging from 1 to 1000 Hz with maximum field strength of 2 tesla, equipped with a novel double-cone coil. The coil was held in position by a specially designed clamp attached to the operating table. Earplugs were inserted during stimulation under baseline conditions and in the awake patient to avoid transient threshold shifts induced by the acoustic stimulus associated with the discharge of the stimulation coil. Resting MEPs were recorded without prior voluntary contraction of the target muscles. Four repetitions were obtained of MEP recordings at each preset stimulation intensity and frequency to assure consistency of the results. The SPL at threshold (T) and suprathreshold (T + 10%, T + 30%) stimulation intensities, DPS, and QPS, both at T + 30% and 500 Hz, were used in our study. Threshold intensity was defined as the stimulation amplitude producing a myogenic potential of 50 μV or higher in at least 50% of 10 repetitive SPSS. The CMAP amplitudes were measured from peak to peak, whereas latencies were defined as the interval between the stimulation artifact and the onset of the CMAP.

Statistical Analysis

Data are expressed as the mean ± SD or as the median and range in those instances in which there is substantial deviation from the normal distribution of data. Two-sample significance of data was tested using the Mann–Whitney U-test. Analysis of variance (Kruskal–Wallis test) was used to describe differences in distribution among the various groups. Statistical significance was assumed for probability values less than 0.05. All statistical analyses were performed using commercially available scientific statistics software.

Sources of Supplies and Equipment

The ventilator used for the rabbits (model CIV 101) was purchased from Columbus Instruments, Columbus, OH. The monitor for end-tidal CO2 (model CS/3) was manufactured by Datex-Ohmeda, Duisburg, Germany. The voltage stimulator (Digitimer D180) was obtained from Digitimer Ltd., Hertfordshire, UK. The remifentanil was obtained from Glaxo-Wellcome, Bad Oldesloe, Germany. The IVA-SIM software (TCI/TIVA 9000) was acquired from Alaris Medical Systems, Hampshire, UK, as was the TCI system. The Diprifusor module incorporated in the TCI system and used for target-controlled administration of propofol was purchased from Zeneqa Pharmaceuticals, Cheshire, UK. The propofol was obtained from AstraZeneca, Weddington, NC.

The electrophysiological equipment (Spirit EP System) was purchased from Nicolet Biomedical, Madison, WI. The multipulse magnetic stimulation device (Magstim Quadropulse 500) was supplied by Inomed, Teningen, Germany. The statistical software (Statistica 5.0) was obtained from StatSoft, Hamburg, Germany.
Results

Experimental Findings

Opioids: Alfentanil, Sufentanil, Fentanyl, and Remifentanil. Each of these opioid anesthetic agents was delivered incrementally to groups of 10 rabbits via both single-bolus administration and continuous infusion, until defined dosage end points (surgical anesthetic depth and extinction of myogenic MEPs, respectively) were obtained. For bolus administration, fentanyl was given at 15 μg/kg bw, alfentanil at 150 μg/kg bw, and sufentanil at 1.5 μg/kg bw. The opioid bolus dosage regimens used in our animal experiments reflect those recommended in current clinical induction protocols. Tolerance of surgical manipulation (lowered heart rate and EEG response to an abdominal and plantar skin incision) and controlled ventilation was observed after bolus administration. Nevertheless, significant suppression of myogenic MEPs (p < 0.01) resulted at this level of anesthesia. The most pronounced reduction of MEP amplitude, to 42% of baseline values (41.6 ± 18.5%), was recorded following fentanyl administration, whereas the least suppressive effect resulted from sufentanil administration (57 ± 20%). Alfentanil ranged between fentanyl and sufentanil (51.8 ± 31%) in its attenuation of myogenic potentials. Maximum suppression of myogenic MEPs from fentanyl was observed at 6 minutes after bolus administration, whereas corresponding effects were registered 2 minutes after alfentanil and 4 minutes after sufentanil bolus administration. Return to baseline amplitude levels was complete at 18 (fentanyl), 16 (alfentanil), and 12 minutes (sufentanil) after bolus administration (Fig. 1). The latencies of myogenic responses were significantly increased (p < 0.05) following both fentanyl and alfentanil bolus administration (fentanyl 105% and alfentanil 107% of baseline latencies). No significant effects were recorded after sufentanil infusion. Neurogenic responses (that is, ESCPs) were significantly affected only by fentanyl, with a mean reduction of ESCP amplitude to 86% of baseline levels (p < 0.05). The ESCP amplitude remained essentially unaltered following administration of both alfentanil and sufentanil.

In addition to bolus administration, fentanyl, alfentanil, sufentanil, and remifentanil (Ultiva, a new ultra-short-acting opioid medication with a clinical halflife of 3 to 10 minutes suitable for administration through computerized TCI devices) were infused continuously, starting at 75 μg/kg bw/min (alfentanil), 40 μg/kg bw/min (fentanyl), 5 μg/kg bw/min (sufentanil), and 0.5 μg/kg bw/min (remifentanil; calculated target plasma concentration approximately 12.5 ng/ml). The infusion rate was adjusted incrementally to achieve two defined dosage end points: surgical anesthetic depth and complete suppression of myogenic responses, respectively. Nevertheless, MEPs were not abolished, even at high remifentanil infusion rates of 10 μg/kg bw/min. The incremental adjustments were done to evaluate and eliminate nonspecific effects of bolus administration on potential findings, effects caused by inadvertent modulation of blood flow to muscles or transient influences on central or neuromuscular signal transduction. Under the steady-state conditions offered by continuous infusion, ESCP and CMAP amplitudes observed during surgical anesthesia resembled those seen after a dose-equivalent bolus administration (fentanyl, alfentanil, sufentanil). In contrast, remifentanil administered at 0.5 μg/kg bw/min induced surgical anesthesia (no heart rate response to skin incision, tolerance of controlled ventilation) in all animals with no suppressive effects on either neurogenic or myogenic MEPs. Subsequently, the infusion rate was increased 20-fold.

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Responses of each opioid that allows intraoperative recording of myogenic reduction of surgical anesthetic depth (remifentanil). The concentration ratio (plasma level inducing loss of myogenic MEPs divided by plasma concentration related to induction of surgical anesthetic depth) represents the dosage interval of each opioid that allows intraoperative recording of myogenic responses.

Sufentanil, only moderate suppression of myogenic responses (51.4 ± 27.1% of baseline CMAP amplitude) was observed, even at excessive infusion rates of 10 µg remifentanil/kg bw/min; neurogenic potentials remained unaltered. Analysis of opioid plasma concentrations at levels that induced surgical anesthesia and loss of myogenic MEPs, respectively, reveals narrow dosage intervals suitable for intraoperative recording of myogenic MEPs for fentanyl, alfentanil, and sufentanil, but not remifentanil (Fig. 2). The plasma concentration ratio between surgical anesthetic depth and CMAP suppression was 2.2 for fentanyl and alfentanil, compared with 2.6 for sufentanil. The target plasma concentration ratio between surgical anesthetic depth and 50% reduction of CMAP baseline amplitudes was 20 for remifentanil. Thus, remifentanil has a much wider dosage window with respect to recording of myogenic MEPs than all other opioids investigated so far. No drug accumulation has to be considered even after prolonged application, due to the extremely short halflife of remifentanil (clinical halflife in humans 3–10 minutes, in rabbits 2–5 minutes).

Thiopental and Brevimytal. Both barbiturates were administered as single boluses, to 10 animals each at typical induction doses of 2 mg/kg bw and as continuous infusions to induce an EEG burst–suppression pattern. Boluses of 2 mg/kg bw thiopental induced both apnea and tolerance to surgical manipulation with no significant effects on latency or amplitude of either neurogenic or myogenic MEPs, whereas significant increases of CMAP and ESCP amplitudes were observed after injection of 2 mg/kg bw brevimytal (p < 0.01). This effect may be attributable to the general increase in neuronal excitability induced by brevimytal at low doses, which has been used to activate epileptogenic foci. High plasma levels of barbiturates that induce burst suppression on EEG studies significantly reduce myogenic responses (p < 0.01), however, and increase latencies of both ESCP and CMAP. Therefore, the main modulating effect of both barbiturates on MEPs appears to depend mainly on suppression of cortical activity.

Midazolam. Midazolam was administered as a single bolus by using a typical clinical induction dose of 0.2 mg/kg bw in 15 rabbits. All animals tolerated both surgical manipulation and controlled ventilation following single-bolus application; significant effects were not observed on either ESCP or myogenic MEP (p > 0.1).

Etomidate. Etomidate was administered both as a single bolus at typical induction doses of 0.2 mg/kg bw and as a continuous infusion adjusted to induce burst suppression on EEG studies in a total of 15 animals. Bolus administration of 0.2 mg/kg bw induced hypnosis, but not surgical anesthesia or tolerance to controlled ventilation. No significant effects on either myogenic or neurogenic potentials were observed at induction doses of etomidate. Whereas burst–suppression doses of etomidate generally induce apnea and tolerance to surgical manipulation, no significant changes of CMAP and ESCP became apparent, even during suppression of electrocortical activity.

Ketamine. Ketamine was administered in incremental doses (2, 4, and 8 mg/kg bw) in 15 rabbits. Surgical manipulation was well tolerated after bolus administration of 2 mg/kg bw, and all animals maintained sufficient spontaneous ventilation. No significant changes of either CMAP or ESCP amplitudes or latencies were observed. Increasing the bolus dose to 4 mg/kg bw led to a significant reduction (p < 0.01) of CMAP amplitudes in the fore- and hindlimbs (60 ± 31% of baseline values), commensurate with increasing CMAP latency (0.3 msec, not significant). Sufficient spontaneous ventilation was maintained at up to 4 mg/kg bw. Dose escalation to 8 mg/kg bw was associated with further reduction of CMAP amplitudes to 45 ± 32% of baseline (forelimbs) and 27 ± 43% of baseline values (hindlimbs), whereas CMAP latencies were not additionally prolonged compared with bolus administration of 4 mg/kg bw. Intermittent assisted ventilation was mandatory, however, to maintain stable PaO2 and PaCO2 following bolus administration of 8 mg/kg bw ketamine. The ESCP amplitudes and latencies, as well as the number of l-waves, remained constant throughout the dosage range investigated.

Propofol. Propofol was administered as a single bolus of 10 mg/kg bw and then continuously at increasing infusion rates (starting at 5 mg/kg bw/min) until the two dosage end points were reached (surgical anesthesia and suppression of myogenic responses). Tolerance to surgical manipulation as well as controlled ventilation (surgical anesthesia) was induced by bolus administration of 10 mg/kg bw. The MEPs recorded from different muscle groups of the forelimbs (CMAPs) were significantly reduced, to 29 ± 97% of baseline (p < 0.01), whereas myogenic responses were completely suppressed at the hindlimbs. Baseline amplitudes were restored after 7 to 8 minutes at the forelimbs and 10 to 15 minutes at the hindlimbs, respectively (Fig. 3). The CMAP latencies were not significantly prolonged at the forelimbs; however, a significant increase of CMAP latencies was observed during the initial recovery phase of myogenic MEPs at the hindlimbs 5 minutes after bolus administration (p < 0.01). In contrast, ESCPs recorded at the upper and lower thoracic spinal cord were not significantly increased.
attenuated after administration of 10 mg/kg bw propofol. Continuous administration of propofol at infusion rates that induced surgical anesthesia reduced MEP amplitudes at the forelimbs to 57/100%, 65% of baseline levels (p < 0.01), whereas myogenic MEPs were completely abolished in the hindlimbs. Again, ESCP amplitudes and latencies were not significantly altered (p > 0.1).

Clinical Findings

**Propofol.** Propofol was administered continuously via a computerized TCI system to a number of preset incremental target plasma concentrations (1, 3, and 6 μg/ml). Average target plasma concentrations of 3 ± 0.8 μg/ml were required to induce loss of responsiveness in 50% of patients; 5 ± 1 μg/ml (range 4–6 μg/ml) were needed to induce surgical anesthesia (loss of responsiveness in 95% of patients, tolerance to laryngoscopy). Significant suppression of myogenic MEPs (p > 0.01) was observed during stepwise escalation of propofol plasma concentration (Fig. 4). The CMAP amplitudes were reduced to less than 20% of baseline at only 2 μg/ml, regardless of stimulation intensity and frequency. The CMAPs elicited by SPS and low stimulation intensities near threshold (T, T + 10%) were obtainable only in conscious patients (propofol target plasma concentrations ≥ 3 μg/ml). Concomitant to loss of responsiveness in 50% of patients (propofol plasma concentrations ≥ 3 μg/ml), supramaximal stimulation intensities (SPS, T + 30%) or multipulse stimulation (QPS) were necessary to elicit reproducible MEPs. The CMAP latencies and number of MEP phases were not significantly influenced by either stimulation intensity or different propofol plasma concentrations.

**Remifentanil.** Remifentanil administered continuously via a computerized TCI system to target plasma concentrations of 3, 9, 12, and 15 ng/ml also induced a dose-dependent suppression of myogenic MEPs (Fig. 5). On average, target plasma concentrations of 9 ± 1.4 ng/ml were required to induce loss of responsiveness in 50% of patients, and 12 ± 3.8 ng/ml (range 9–15 ng/ml) were needed to induce surgical anesthesia (loss of responsiveness in 95% of patients, tolerance to laryngoscopy). The CMAP amplitudes were reduced to 50% of baseline at target plasma levels of 9 ng/ml. Similar to the findings obtained after propofol administration, maximum CMAP amplitudes were registered after QPS at 500 Hz. The overall suppressive effect of remifentanil was far less marked, however. Consistent MEP recordings were obtained following SPS, even at target plasma concentrations of up to 15 ng/ml (Fig. 5). The CMAP latencies were not significantly altered by increasing the doses of remifentanil. Analogous to the observations made during propofol application, progressive polyphasia of myogenic responses was noted during QPS.

Discussion

Although neurogenic potentials from the spinal cord or peripheral neural structures are far less affected by anesthesia, recording these potentials requires invasive placement of electrodes and is therefore not routinely used in clinical practice. For this reason, a wealth of stimulation methods, including different facilitation paradigms as well as repetitive stimulation, has been applied to MEP monitoring to increase the reliability of myogenic MEPs. The influence of anesthesia on MEPs, however, mainly in the registration of myogenic potentials, has prevented the widespread use of MEPs in routine intraoperative electrophysiological monitoring. This is especially true in recording MEPs of already reduced quality in neurosurgical procedures.
gical patients with preexisting neurological deficits caused by intramedullary lesions or degenerative changes of the cervical spine. In our study, the effects of alfentanil, sufentanil, fentanyl, remifentanil, barbiturates, midazolam, etomidate, ketamine, and propofol on neurogenic and myogenic MEPs were evaluated by combining clinical data obtained in 40 patients with experimental investigations in 140 animals.

Experimental Results

Highly consistent data were obtained during our experimental study in rabbits. Intraindividual and interindividu-
al variability of the responses to transcranial electric stimulation recorded both from the spinal cord through bipolar electrodes placed at different levels of the thoracic spinal canal, and from the extremity muscles, was acceptably low (absolute changes in amplitudes and latencies usually ranged within 2 SDs). Meticulous care was taken to maintain constant physiological conditions (MABP, body temperature, PaCO2) during the experiments to eliminate alteration of electrophysiological parameters other than those directly related to modulation of the motor system. Because intravenously administered anesthetic agents act on different levels of the motor system, from the cortex down to the neuromuscular junction, avoidance of systemic influences (as far as possible) is mandatory to assure correct interpretation of potential findings. The marked reduction of CMAPs observed after bolus administration of propofol, which led to a significant suppression of myogenic potentials (probably resulting from decreased blood flow to muscles) underscores the importance of minimizing such confounding factors.

Transfer of experimental findings to the clinical setting is one of the most important aspects in evaluating the usefulness of an animal model. In our study, we found excellent correlation between experimental and clinical findings for all anesthetic drugs investigated. In most cases, electrophysiological effects in humans and rabbits were comparable at similar or equal anesthetic dosage regimens. These findings proved to be very helpful in the process of estimating the dose-response curve of individual anesthetic drugs and designing suitable dose escalation schemes for both experimental and clinical investigations.

Clinical Results

Dose-dependent suppression of myogenic potentials elicited by transcranial magneto-electric stimulation of the motor cortex was observed during incremental administration of propofol and remifentanil. At average propofol target plasma concentrations of more than 3 µg/ml, stable
recording of CMAPs from muscles in the extremities requires both supramaximal stimulation intensities and QPS. Similarly, remifentanil suppresses myogenic MEPs in a dose-dependent fashion; however, its suppressive effect on CMAP amplitudes is rather moderate compared with propofol, and, remarkably, all other opioids investigated in our series. Due to their short context-sensitive halflife, both substances are well suited for neurosurgical procedures in which early postoperative emergence from anesthesia is desirable.

With respect to CMAP amplitudes, the most effective stimulation frequency at medium and high anesthetic target plasma concentrations was QPS at 500 Hz and supramaximal stimulus amplitudes (T + 30%). Further research is warranted to determine the ideal stimulation frequency and pulse number for intraoperative MEP monitoring during surgical anesthesia, possibly with additional administration of muscle-relaxing drugs.

Choosing an Appropriate Anesthetic Protocol for MEP Monitoring

Opioids are widely used in neurosurgical anesthesia because they offer well-characterized anesthetic properties without significant influences on systemic and cerebral circulation. Nevertheless, their effective plasma concentration range allowing intraoperative monitoring of MEPs is quite narrow, with significant potential suppression observed even after slight increases in the infusion rate. Therefore, total intravenous anesthesia incorporating fentanyl, sufentanil, and alfentanil is feasible, yet not particularly suitable for maintaining stable intraoperative potentials, which makes interpretation of findings regarding potentials problematic. In contrast, remifentanil has major advantages with respect to both anesthetic and neurophysiological properties. Its extremely short halflife allows continuous administration by TCI systems, maintaining constant plasma concentrations. Because the effect of remifentanil on MEPs remains stable during continuous infusion at a given infusion rate, it may be presumed that the concentration within the central nervous system also remains constant.

At our institution, etomidate and barbiturates are not currently in routine use to maintain surgical anesthesia, but only as induction agents. Quite favorable results with respect to preservation of MEPs were obtained, however, in a study by Lee, et al., in which etomidate was used in a combination to induce total intravenous anesthesia.

Whereas continuous application of barbiturates may lead to drug accumulation, causing unwanted prolongation of anesthesia and preventing early postoperative neurological
evaluation of the patient, etomidate has been shown to suppress adrenal function after continuous administration. In clinical studies significant reductions in CMAP amplitudes have been demonstrated during induction of anesthesia with thiopental and methohexital following magnetoelectric stimulation, even in awake patients. During steady-state conditions, MEPs remained intact in 50% of the patients who received methohexital and only 20% of the patients who received thiopental. Our own experiences with these two barbiturates indicate that supplemental low-dose administration of methohexital may be quite useful for maintaining both adequate hypnosis and stable MEPs during total intravenous anesthesia in which remifentanil is used (unpublished data). Similarly, Watt, et al., recorded stable myogenic potentials in patients in whom total intravenous anesthesia was induced with methohexital, alfentanil, and ketamine.

In our own as well as other studies, ketamine exhibits very favorable neurophysiological properties, but has not been used widely in total intravenous anesthesia for neurosurgical procedures, because it has been believed to increase cerebral blood volume. More recent investigations have demonstrated, however, that this effect may be easily eliminated and therefore does not preclude the use of ketamine in total intravenous anesthesia for neurosurgical procedures. Ketamine induces a dose-dependent suppression of myogenic MEPs with concomitant prolongation of CMAP latency, yet with no effect on neurogenic responses recorded from the spinal cord. Therefore, inhibition at the α-motor neuron or the neuromuscular junction may account for the effects on myogenic responses observed in our study. In contrast, midazolam is routinely used for total intravenous anesthesia and analgesia and sedation in neurosurgical patients in the operating room and the intensive care unit. It has favorable anesthetic and neurophysiological properties, because it neither significantly influences cerebral perfusion nor suppresses myogenic or neurogenic MEPs. With continuous administration beyond 6 hours, however, significant accumulation occurs, with subsequent prolongation of recovery from anesthesia. Therefore, total intravenous anesthesia during long neurosurgical procedures warrants the use of another sedative if both intraoperative monitoring of the motor system and early postoperative evaluation of the patient is mandatory. In this respect, propofol offers the advantages of a drug with a very short half-life that is suitable for continuous application through TCI. In contrast with midazolam, propofol significantly suppresses myogenic potentials in a dose-dependent fashion. In our series, only target plasma concentrations of up to 4 μg/ml allowed reliable intraoperative interpretation of myogenic MEPs.

According to the results of our study, total intravenous anesthesia that incorporates remifentanil and midazolam appears to provide the most favorable anesthetic and neurophysiological properties for intraoperative recording of myogenic MEPs. For lengthy procedures, propofol may be substituted for midazolam to prevent drug accumulation. If propofol has to be administered at concentrations that prohibit reliable intraoperative CMAP recording, midazolam may be substituted at those stages of the operation during which monitoring is required.

Generally, the use of TCI systems for total intravenous anesthesia during neurosurgical procedures will significantly aid in predicting the impact of anesthetic agents on both circulatory and neurophysiological parameters. For this reason, it will greatly enhance the reliability of intraoperative findings regarding potentials, and thus improve the quality of intraoperative assessment of the motor system.

References
Total intravenous anesthesia and motor evoked potentials


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