Differential effects of nitrous oxide and propofol on myogenic transcranial motor evoked responses during sufentanil anaesthesia†

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Summary
We have compared the effects of 50% nitrous oxide and propofol, each administered concurrently with sufentanil, on the amplitudes and latencies of the compound muscle action potential (CMAP) response to transcranial electrical stimulation. Using a crossover design, 12 patients undergoing spinal surgery were exposed to both 50% nitrous oxide and propofol, the latter in a bolus–infusion regimen. Six patients received nitrous oxide first and six received propofol first. CMAP were recorded from the tibialis anterior muscle in response to both single and paired transcranial electrical stimuli. With single pulse stimulation, median CMAP amplitude was significantly greater during administration of nitrous oxide than propofol (nitrous oxide 335 (10th–90th percentiles 35–849) μV; propofol 36 (0–251) μV) (P<0.01). With paired stimulation, there was no significant difference in CMAP amplitude during the two regimens (nitrous oxide 1031 (296–1939) μV; propofol 655 (0–1867) μV). The results indicate that propofol caused more depression of transcranial electrical motor evoked responses than 50% nitrous oxide but that the difference was probably clinically unimportant when a paired stimulation paradigm was used. (Br. J. Anaesth. 1997; 79: 590–594).

Key words

Intraoperative monitoring of motor evoked responses to transcranial electrical or magnetic stimulation (tc-MER) provides a method of assessing the integrity of ventral motor columns during operations in which there is a risk of spinal cord injury.

A difficulty with intraoperative tc-MER monitoring lies in the considerable tc-MER amplitude depression that occurs with most anaesthetic regimens. At least with single stimuli, the use of relatively low concentrations of volatile anaesthetics (0.2–0.3% end-tidal isoflurane1 2) precludes intraoperative tc-MER monitoring. Nitrous oxide3 benzodiazepines,4 5 barbiturates and propofol5 have been shown to depress tc-MER amplitude. Drugs that have been shown to have only minor effects on tc-MER are those known to maintain or increase muscle tone, for example etomidate,7 ketamine and synthetic opioids.5

Currently, two anaesthetic regimens are used widely during surgery in which myogenic responses to transcranial stimulation are used for spinal cord motor tract monitoring. Some groups have successfully used nitrous oxide–opioid anaesthesia.2 3 6 Others have advocated propofol–opioid total i.v. anaesthesia (TIVA).7 These two anaesthetic techniques have not been compared previously with respect to the relative magnitude of tc-MER depression.

The purpose of this crossover study was to determine the relative effects of nitrous oxide and propofol on tc-MER amplitude, amplitude variability and onset latencies. As it was shown recently that multiple stimuli may improve the efficiency of transcranial stimulation,8–11 comparison of the two anaesthetic regimens was performed with both single and paired stimuli.

Patients and methods
Written informed consent for this institutionally approved study was obtained from 12 patients (seven females, aged 14–64 yr) undergoing orthopaedic spinal surgery.

Transcranial stimulation was performed using two identical Digitimer D180A transcranial electrical stimulators (Digitimer Ltd, Welwyn Garden City, UK), triggered either simultaneously (single pulse stimulation) or sequentially with an inter-stimulus interval of 3 ms (paired stimulation). The outputs from both units were combined via diodes and delivered to the scalp via 9-mm silver EEG disk...
Effects of propofol and \text{N}_2\text{O} on evoked responses

Each patient was questioned specifically for recall of intraoperative events immediately after surgery and on the following day.

**Results**

Figure 1 shows representative triplicate CMAP to paired and single pulse transcranial stimulation during both anaesthetic regimens in one patient.

**SINGLE PULSE STIMULATION**

During nitrous oxide–opioid anaesthesia, reproducible responses with single transcranial stimuli were recorded in 11 of 12 patients, whereas during propofol–opioid TIVA, tc-MER were recordable in seven of 12 patients. During the nitrous oxide regimen, tc-MER amplitude was 335 (35–849) \( \mu \text{V} \) and latency to onset 33.9 (3.9) ms. With propofol, tc-MER amplitude was 36 (0–251) \( \mu \text{V} \) (\( P < 0.01 \)) and latency 34.3 (3.4) ms. There was no significant difference in onset latency between the two anaesthetic regimens.

**PAIRED STIMULATION**

During nitrous oxide–opioid anaesthesia, tc-MER to paired stimulation were recordable in all patients, whereas tc-MER during propofol–opioid anaesthesia were elicited in 10 of 12 patients with paired stimuli. There was no significant difference in amplitude or onset latency between the two anaesthetic regimens. During the nitrous oxide regimen, tc-MER

\[ \text{Compound muscle action potentials (CMAP) to single and paired stimulation were acquired in a 1-min period every 3 min during the study. For each regimen and stimulation paradigm, the median amplitude from 10 responses, recorded every 3 min, was calculated and compared using the Wilcoxon signed rank test. Amplitudes are presented as median (10th and 90th percentiles) and latencies as mean (SD).} \]

To estimate with-patient variability, we calculated the coefficient of variation (cv) from 10 responses. The cv were compared using the Wilcoxon signed rank test and are expressed as median (10th and 90th percentiles).

In both groups anaesthesia was induced with etomidate 0.3 mg kg\(^{-1}\) and a loading dose of sufentanil 1.5 \( \mu \text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1} \), followed by continuous infusion of 0.5 \( \mu \text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1} \). Intubation of the trachea was facilitated with vecuronium 0.1 mg kg\(^{-1}\).

Neuromuscular block was monitored electromyographically at the hypothenar eminence using a Datex Relaxograph (Datex, Finland). This device applies a train-of-four stimulus to the ulnar nerve every 20 s and displays the height of the first response (T1%), and the train-of-four ratio (T4/T1%). After the amplitude of T1 had recovered to 20% of control, neuromuscular block was maintained at this level throughout surgery with vecuronium using a closed-loop infusion system. This level of neuromuscular block at the hypothenar muscle produces a T1 of 60% at the tibial anterior muscle.\(^{11}\)

Routine anaesthetic monitoring included ECG, S\(_{\text{PO}_2}\), invasive arterial pressure, central venous pressure, end-tidal carbon dioxide concentration and nasopharyngeal temperature.

The order in which patients received nitrous oxide or propofol was randomized. After induction of anaesthesia, 50% of patients received 50% nitrous oxide in oxygen until 60 min after skin incision. Thereafter, administration of nitrous oxide was discontinued and propofol 1 mg kg\(^{-1}\) administered i.v., followed by an infusion at a rate of 10 mg kg\(^{-1}\) h\(^{-1}\) for the first 10 min, 8 mg kg\(^{-1}\) h\(^{-1}\) for the next 10 min and 6 mg kg\(^{-1}\) h\(^{-1}\) for the remainder of the procedure. This infusion results in blood propofol concentrations of approximately 3 \( \mu \text{g} \cdot \text{ml}^{-1} \).\(^{14}\)

Nitrous oxide

- Propofol

\[ \text{Single pulse} \]

\[ \text{Paired stimulation} \]

\[ 0.5 \text{ mV} \]

\[ \text{Nitrous oxide} \]

\[ \text{Propofol} \]

\[ \text{CMAP to paired and single pulse transcranial stimulation, during both anaesthetic regimens (nitrous oxide and propofol), in a patient undergoing orthopaedic spinal surgery. TriPLICATE responses are superimposed to indicate reproducibility.} \]
amplitude was 1031 (296–1939) µV and latency 30.8 (2.3) ms. With propofol, tc-MER amplitude was 655 (0–1867) µV and latency 29.6 (2.3) ms.

With both anaesthetic regimens, tc-MER amplitude was significantly higher when paired transcranial stimulation was used ($P<0.01$) and onset latency was shorter ($P<0.01$). Figure 2 shows box plots of tibialis anterior tc-MER to single pulse and paired transcranial stimulation during both anaesthetic techniques.

There was no significant difference in the coefficient of variation for tc-MER amplitude between the two anaesthetic regimens (fig. 3). For the nitrous oxide–opioid regimen, $\text{cv}$ was significantly less ($P<0.05$) with paired stimuli than with a single stimulus. During the propofol–opioid regimen there was a tendency ($P=0.08$) to a smaller $\text{cv}$ with paired stimulation. With a single stimulus, the $\text{cv}$ was 32% (12–85%) during nitrous oxide–opioid anaesthesia and 42% (15–190%) during propofol–opioid TIVA. When paired stimuli were used, the $\text{cv}$ was 8% (18–71%) during nitrous oxide–opioid anaesthesia and 14% (9–57%) during propofol–opioid TIVA.

During the recording period, haemodynamic variables remained stable and there was no significant difference in heart rate (HR) or mean arterial pressure (MAP) between the two anaesthetic regimens. During propofol–opioid anaesthesia, mean HR was 76 (SD 6.4) beat min$^{-1}$ and MAP 83 (10.1) mm Hg; during nitrous oxide–opioid anaesthesia, HR was 78 (8.2) beat min$^{-1}$ and MAP 81 (12.3) mm Hg. None of the patients experienced recall of intraoperative events.

**Discussion**

The data derived from this study indicate that at the doses used, propofol–opioid TIVA depressed the amplitude of myogenic responses to electrical transcranial stimulation more than nitrous oxide–opioid anaesthesia. Although there was no significant difference in amplitude between both anaesthetic regimens when paired transcranial stimuli were used, tc-MER were not recordable in two of 12 patients during propofol, while during nitrous oxide, tc-MER were recordable in all patients. Although nitrous oxide is a potent depressant of myogenic tc-MER, most authors were successful in obtaining reproducible myogenic responses to transcranial stimulation, provided relatively low concentrations of nitrous oxide were used. Zentner and Ebner have examined the effects of increasing nitrous oxide concentrations on motor evoked responses to cortical and mid-cervical electrical stimulation, recorded from the thigh muscles in six rats. They observed a 45% reduction in amplitude with an end-tidal nitrous oxide concentration of 50% at 66% end-tidal nitrous oxide, the myogenic signal was completely abolished.

Ghaly and co-workers have examined the effects of nitrous oxide on magnetic tc-MER recorded from the fore- and hindlimb flexor muscles in 16 cynomolgus monkeys. They were able to record tc-MER in all animals with nitrous oxide concentrations up to 75%. However, with 75% end-tidal nitrous oxide, tc-MER amplitude was significantly decreased and stimulation threshold intensity increased, compared with 25% and 50% end-tidal nitrous oxide.

Woodforth and colleagues studied variability of tibialis anterior tc-MER to electrical stimulation in six patients undergoing surgery for correction of scoliosis. Anaesthesia was maintained with fentanyl and 70% nitrous oxide in oxygen. The authors recorded responses to single pulse stimulation in all patients although amplitude was very low (mean of 100 responses $<$50 µV in all patients). However, with these high concentrations nitrous oxide tc-MER amplitude is depressed substantially and variability increases to such an extent that reliable spinal cord monitoring may not be possible.

In contrast, most studies which have described clinical tc-MER monitoring during propofol anaesthesia showed a smaller success rate in obtaining a reproducible myogenic response. Kalkman and co-workers examined the effects of a bolus dose of propofol 2 mg kg$^{-1}$ on electrical and magnetic tibialis anterior tc-MER in five healthy volunteers.
Two minutes after administration of propofol tc-MER amplitude decreased to 2.2 (SD 0.9)% of baseline; 30 min after administration, tc-MER amplitude was still depressed (44 (18)%). There was no effect on onset latency.

Jellinek, Jewkes and Symon studied tc-MER in 26 patients undergoing surgery for a unilateral prolated disc during propofol TIVA. CMAP to electrical transcranial stimulation were recorded from the first dorsal interosseous muscle of the foot of the asymptomatic leg or from the second dorsal interosseous muscle of the hand. After an induction dose of 2 mg kg⁻¹, anaesthesia was maintained with a continuous infusion at a rate of 10–12 mg kg⁻¹ h⁻¹. They were able to elicit reproducible tc-MER in 23 of 26 patients (88.5%), but tc-MER amplitude was 7% of awake control values (obtained with a magnetic transcranial stimulator).

Taniguchi and colleagues studied the effects of propofol on magnetic tc-MER recorded from the abductor pollicis brevis muscle in 22 patients undergoing surgery for lumbar disc herniations. They used a fixed infusion scheme, designed to reach a plasma propofol concentration of 1.5 μg ml⁻¹ within 15 min. Fifteen minutes after the start of propofol infusion (cumulative dose 128 mg) tc-MER were preserved in only three of 22 cases (14%). Jones and colleagues were able to record reproducible myogenic responses of at least 100 μV to trains of three to six transcranial responses during propofol–nitrous oxide–alfentanil anaesthesia, whereas single pulse stimulation failed to elicit reproducible responses.

It is conceivable that the propofol–opioid and the nitrous oxide–opioid regimens were not equipotent and that the propofol–opioid regimen used in this study provided a deeper level of anaesthesia than the nitrous oxide–opioid technique. This could explain the observed difference in tc-MER amplitudes during both anaesthetic regimens. It is likely that a deeper level of anaesthesia results in more amplitude depression because most anaesthetics that depress tc-MER do so in a dose-dependent manner. Unfortunately, there is no method to reliably quantify the “level of anaesthesia” in a clinical setting and we are therefore unable to determine if the observed differences in tc-MER depression were the result of a difference in depth of anaesthesia. The analgesic component consisted of constant infusions of sufentanil and was similar in both regimens. Inadequate anaesthesia, as suggested by increases in heart rate and arterial pressure, did not occur during each regimen and no patient had recall of intraoperative events.

This study confirms previous results that the use of paired transcranial stimulation partly overcomes the anaesthetic-induced depression of the myogenic response during nitrous oxide–opioid and isoflurane anaesthesia. The observed amplitude augmentation with paired stimuli is most likely the result of temporal summation; the first stimulus lowers the excitation threshold of the cortical and spinal motor neurones, thereby facilitating initiation of neuronal discharge by the second stimulus. It is conceivable that stimulation with more than two successive pulses might further increase intraoperative tc-MER amplitudes and result in a greater success rate of tc-MER monitoring during propofol–opioid anaesthesia. Kawaguchi and co-workers described the effects of single pulse and train-of-five electrical stimulation of the exposed motor cortex on the tibialis anterior myogenic response during an anaesthetic regimen consisting of nitrous oxide and isoflurane or sevoflurane. With train-of-five stimulation they were able to record tc-MER in all patients with concentrations of the volatile anaesthetic up to 1.5 times the minimum alveolar concentration.

The results of this study also suggest that the reproducibility of myogenic tc-MER increases when paired stimuli are used. Within-patient variability, expressed as cv, decreased when two pulses were used; this decrease was more pronounced during nitrous oxide–opioid anaesthesia than during propofol–opioid TIVA. It is likely that the decrease in cv during opioid–propofol TIVA was not statistically significant because of the small number of patients analysed (five patients had no response to a single stimulus during TIVA). It is conceivable that reproducibility increases because a higher tc-MER amplitude is obtained that is closer to the maximal response that can be obtained (the CMAP that results when all motor units are discharged).

In summary, we have demonstrated that during propofol–opioid TIVA, muscle responses to electrical transcranial stimulation were depressed more than during nitrous oxide–opioid anaesthesia. However, when paired stimulation was used, responses during both anaesthetic regimens were amplified considerably and the difference became clinically irrelevant in most patients. This suggests that when tc-MER monitoring is indicated, and there is concern about the adequacy of nitrous oxide–opioid anaesthesia, it is possible to use propofol–opioid TIVA, provided that a multiple stimulus paradigm is used. In a subset of patients, propofol–opioid TIVA may depress the motoneural system to such an extent that recordable tc-MER cannot be obtained, even when paired stimuli are used. When this occurs propofol may be substituted by nitrous oxide to allow tc-MER monitoring during stages of surgery in which spinal cord monitoring is imperative. Furthermore, it is likely that the use of more than two successive stimuli may increase the success rate of intraoperative tc-MER monitoring during propofol–opioid TIVA. The results of this study justify further clinical evaluation of the efficacy of multi-pulse transcranial stimulation during total i.v. anaesthesia.

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References


