Influence of propofol concentrations on multipulse transcranial motor evoked potentials

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Background. Motor evoked potentials can be affected by propofol anaesthesia. We studied how increasing target concentrations of propofol altered transcranial motor evoked potentials (tcMEP) during scoliosis surgery.

Methods. Fifteen patients undergoing surgery for scoliosis were anaesthetized with remifentanil and propofol without nitrous oxide or neuromuscular blocking agents (BIS<60). tcMEP were elicited by transcranial electric multipulse stimulation of the motor cortex and recording of compound action potentials from the anterior tibialis muscle. tcMEP were obtained before surgery with propofol target values set from 4 to 8 mg litre⁻¹, and then during surgery. Arterial propofol concentrations were measured for each tcMEP recording.

Results. Before surgery, increasing propofol reduced tcMEP amplitude in a dose-dependent manner, with no effect on latency. During surgery, at equivalent propofol concentrations, tcMEP were not statistically different from those obtained before surgery. In all except one patient, tcMEP signals were present during the entire procedure. In this patient the loss of tcMEP was unfortunately related to an anterior spinal cord lesion, which was confirmed by a wake-up test.

Conclusion. We found that, although propofol had a dose-dependent effect on tcMEP amplitude, anaesthesia could be maintained with remifentanil and propofol to allow recording and interpretation of tcMEP signals.


Keywords: anaesthetics i.v., propofol; analgesics opioid, remifentanil; monitoring, evoked potential; surgery, spinal

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Injury to the spinal cord is a serious risk during spinal surgery and can be detected by appropriate monitoring. Because injury to the spinal cord can occur only in the anterior parts, somatosensory evoked potential (SEP) monitoring may not detect injury of the anterior motor pathway. Loss of motor function can occur after spinal injury despite no changes in recording of SEP,1 suggesting that this type of monitoring cannot detect motor damage.2 3 Many centres advocate monitoring motor evoked potentials (MEP) to assess the motor pathway and avoid the need for a wake-up test. A report of paraplegia, despite normal MEP obtained by direct stimulation of the spinal cord, suggests that MEP should be measured using transcranial stimulation of the motor cortex (tcMEP).4 However, tcMEP recordings are markedly affected by anaesthetics such as nitrous oxide, barbiturates and halogenated agents and also by neuromuscular blocking agents, hypothermia and variations of blood carbon dioxide.5 6 Propofol in low doses decreases the amplitude of the early components of the SEP,7 but its effects on MEP have not been fully investigated5 8 9 so we
studied the effects of increasing doses of propofol on MEP evoked by transcranial electric stimulation of the motor cortex.

Patients and methods

After local ethical committee approval, and with written informed consent, we recruited 15 patients undergoing surgery on the spine with evoked motor potential (MEP) monitoring. The day before surgery, MEP were obtained from all patients. After 1 mg kg\(^{-1}\) hydroxyzine orally 2 h before surgery, anaesthesia was induced with remifentanil (1 \(\mu\)g kg\(^{-1}\) i.v. followed by 0.25–0.4 \(\mu\)g kg\(^{-1}\) min\(^{-1}\) by infusion) and a target concentration infusion of propofol set to give 6–8 mg litre\(^{-1}\) (Gepts’ pharmacokinetic model). Measurements of propofol arterial concentrations showed large errors in predicted values in the first three patients. We then used the Marsh’s pharmacokinetic model (Digitimer Diprifusor\textsuperscript{®}, Astra-Zeneca Inc, UK) to target propofol concentrations. ECG, radial arterial and central venous pressure, pulse oximetry and BIS values (Aspect 1000\textsuperscript{®}, frontal montage, Aspect Medical System Inc., Framingham, MA, USA) were measured in all patients. After orotracheal intubation, the ventilator was set to maintain normocapnia and the propofol target concentration was reduced to 4 mg litre\(^{-1}\). Oesophageal temperature was monitored and normothermia was maintained by forced air warming. No patient was given nitrous oxide or neuromuscular blocking agents during anaesthesia. We measured the latency and amplitude of tcMEP before the patient was positioned or surgery started. The tcMEP were elicited by transcranial electric multipulse stimulation (train-of-five square wave stimulations, 2 ms interstimulus interval, 50 \(\mu\)s stimulus duration and 1000 mA intensity) of the motor cortex (Digitimer D185, Hertfordshire, UK). The compound action potentials were obtained from needle electrodes inserted in the anterior tibialis muscle and recorded by an EMG apparatus (Nicolet Spirit, Madison, WI, USA). tcMEP amplitude and latency values were derived automatically by the system and did not depend on the experience of the operator. The same operator performed all the tcMEP measurements. The first measurements of tcMEP were obtained at a 4 mg litre\(^{-1}\) propofol target concentration. The target concentration was then increased by 1 mg litre\(^{-1}\) increments until between 6 and 8 mg litre\(^{-1}\). tcMEP was recorded after an equilibration period in order to allow the predicted site-effects and arterial concentrations to become similar as shown by the Diprifusor\textsuperscript{®} or computer calculations (for Gept’s pharmacokinetics). The equilibration period allowed was 8–10 min before measuring each tcMEP. This equilibration period was the same when we used the Marsh’s pharmacokinetic model since the same \(K_{eo}\) was used in the two models. For each increment of propofol target, arterial pressure, heart rate, \(P_{\text{CO}_2}\) and BIS values were obtained. Increases in target concentrations were discontinued when arterial pressure was decreased by >30% of pre-anaesthetic values, or if BIS values were <30, or if the raw EEG showed burst suppression indicating that anaesthesia was too deep. If the tcMEP was not obtained at the initial 4 mg litre\(^{-1}\) target concentration and if the BIS value was <60, the propofol target concentration was reduced by 1 mg litre\(^{-1}\) decrements until the tcMEP was detected. Slow increases were started again as soon as tcMEP were obtained. If tcMEP were not detected but the BIS value was >60, propofol concentrations were not reduced and a technical problem (such as disconnection of electrodes) was sought. During surgery, after obtaining a set of measurements, the propofol target concentrations were set to obtain a BIS<60. Transcranial tcMEP measurements were repeated immediately after over-distraction and derotation of the spine. SEP were also monitored continuously during the entire surgical procedure. Each time tcMEP were measured, we sampled arterial blood to measure propofol concentrations using high performance liquid chromatography (HPLC) with electrochemical detection and thymol as internal standard. The method is specific for propofol as shown with a diode array method is specific for propofol as shown with a diode array detector and is linear between 0.02 and 10 mg litre\(^{-1}\). At the end of surgery, i.v. morphine was given to all except one patient, who was given intrathecal morphine.

Results are presented as mean (SD) and compared using the Kruskall–Wallis test. Measured concentrations of propofol and the latency or the amplitude of the tcMEP were related by linear regression. Statistical significance was assumed if \(P<0.05\).

Results

None of the 15 patients recruited had any history of epilepsy. The study plan was not completed in four patients and these patients were excluded from statistical analysis. In two of these patients, MEP was only obtained at either one or two concentrations of propofol because of time constraints. In two other patients, tcMEP could not be obtained before surgery although the apparatus was functioning perfectly. In one of these two patients (patient A), when the target concentration of propofol was reduced, the BIS increased and clinical awakening occurred. This patient had been given morphine 1 mg intrathecally. During surgery, tcMEP reappeared about 4 h 30 min after the start of the procedure. After this, we did not give intrathecal morphine to patients. In the other patient (patient B), the initial
4 mg litre\(^{-1}\) target concentration of propofol was reduced, but the BIS value was persistently <60. tcMEP remained undetectable for 3 h. The arterial propofol concentration measured by HPLC was 18.9 mg litre\(^{-1}\), which was four times greater than predicted by Gepts’ pharmacokinetic model. As a consequence, we used the commercially available Marsh pharmacokinetic model (Diprifusor\(\textsuperscript{\textregistered}\)) for subsequent patients. Details of the 11 patients who completed the study are given in Table 1. Time from induction of anaesthesia, BIS values, \(P_{\text{E}}\text{CO}_2\), and oesophageal temperature at each tcMEP recording are shown in Table 2. Greater propofol target concentrations were associated with smaller BIS values (\(P<0.05\), ANOVA). The predicted propofol concentrations of the two patients in whom Gepts’ pharmacokinetic model was used, were calculated according to Marsh’s pharmacokinetic model. Because the measured values were close to the concentrations predicted by this latter model, the data were kept in the analysis. The mean prediction errors (MPE) of propofol concentration and its absolute values (MAPE) are presented in relation to their time of sampling and to the predicted concentration in Table 3. Baseline amplitudes and latencies of tcMEP had considerable variations between subjects (Table 1), so we calculated changes in tcMEP amplitude from baseline to compare data. In two out of 11 patients, the predicted propofol concentration had to be reduced to 3 mg litre\(^{-1}\) to obtain tcMEP and thereafter were increased by 1 mg litre\(^{-1}\) increments. The mean amplitudes of tcMEP, but not their latencies, were significantly reduced by increasing propofol concentrations during stage 1 (Table 4 and Fig. 1). A statistical correlation was found between measured propofol blood concentration and change from baseline of the tcMEP amplitudes recorded on the left side (\(r=-0.68, P<0.001\)) and the right side (\(r=-0.53, P<0.001\); Fig. 2). There was no statistical correlation between blood propofol concentration and tcMEP latencies during stage 1. The amplitude variation of tcMEP [mean (SD)] obtained during surgery reached 34 (63) µV and 65 (86) µV on the left side when propofol concentrations were 3 and 4 mg ml\(^{-1}\) respectively. The corresponding values obtained on the right side were 26 (54) µV and 30 (63) µV at the same propofol concentrations. These values were not statistically different from those obtained during surgery. However, in one patient, both SEP and tcMEP disappeared at the time of rod fixation. In this patient, the use of target concentration infusion of propofol with the combination of remifentanil allowed a rapid wake-up test, which confirmed an anterior spinal cord lesion and the patient unfortunately sustained complete paraplegia. No patients moved unexpectedly during surgery and anaesthesia.

### Discussion

We found that propofol reduced tcMEP amplitude in a dose-dependent manner when using a multipulse stimulation with a constant intensity and number of stimuli. Consequently, an exact knowledge of the effects of increasing propofol concentration on MEP amplitude is needed to avoid the erroneous conclusion that changes in tcMEP amplitude represent spinal cord injury during surgical manipulations. However, tcMEP latencies were not influenced by propofol concentrations commonly used to maintain a deep anaesthesia and remained stable during the whole anaesthesia.

We could obtain tcMEP using multipulse stimulation of the motor pathway, while controlling propofol anaesthesia with Marsh’s pharmacokinetic model in all except two patients. The absence of detectable MEP in the patient who had received high dose intrathecal morphine is unexplained and deserves further study. In the other patient in whom tcMEP were not recorded before surgery, the 18 mg litre\(^{-1}\) propofol concentration suppressed the excitability of cortical and spinal motor neurones. Previous authors found that motoneurone excitability is markedly impaired when target propofol concentrations reach 9 mg litre\(^{-1}\).\(^{11}\) In

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**Table 2** Time elapsed from induction (min), BIS, \(P_{\text{E}}\text{CO}_2\) (mm Hg), oesophageal temperature (°C), systolic and diastolic arterial pressure (mm Hg) and heart rate (beats min\(^{-1}\)) during different predicted propofol concentrations before and during surgery. Data are mean (SD)

<table>
<thead>
<tr>
<th>Predicted concentration (mg litre(^{-1}))</th>
<th>Delay from induction (min)</th>
<th>BIS value</th>
<th>(P_{\text{E}}\text{CO}_2) (mm Hg)</th>
<th>Temperature (°C)</th>
<th>Systolic arterial pressure (mm Hg)</th>
<th>Diastolic arterial pressure (mm Hg)</th>
<th>Heart rate (beats min(^{-1}))</th>
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<td>Before surgery</td>
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<td>4</td>
<td>57 (12)</td>
<td>37 (11)</td>
<td>29 (4)</td>
<td>36.3 (0.6)</td>
<td>98 (14)</td>
<td>55 (12)</td>
<td>70 (18)</td>
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<tr>
<td>5</td>
<td>66 (12)</td>
<td>35 (10)</td>
<td>29 (4)</td>
<td>36.2 (0.6)</td>
<td>101 (12)</td>
<td>57 (12)</td>
<td>64 (9)</td>
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<tr>
<td>6</td>
<td>72 (11)</td>
<td>32 (7)</td>
<td>28 (4)</td>
<td>36.2 (0.6)</td>
<td>99 (14)</td>
<td>56 (13)</td>
<td>65 (10)</td>
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<tr>
<td>7</td>
<td>82 (12)</td>
<td>23 (8)</td>
<td>28 (4)</td>
<td>36.1 (0.8)</td>
<td>99 (18)</td>
<td>58 (10)</td>
<td>64 (7)</td>
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<td>8</td>
<td>92 (14)</td>
<td>23 (8)</td>
<td>30 (3)</td>
<td>36.1 (1.1)</td>
<td>95 (16)</td>
<td>57 (14)</td>
<td>72 (7)</td>
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<tr>
<td>During surgery</td>
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<tr>
<td>3</td>
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<td>46 (16)</td>
<td>29 (2)</td>
<td>36.6 (0.2)</td>
<td>109 (20)</td>
<td>40 (21)</td>
<td>64 (15)</td>
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<tr>
<td>4</td>
<td>246 (48)</td>
<td>39 (8)</td>
<td>28 (3)</td>
<td>36.3 (1.0)</td>
<td>96 (16)</td>
<td>60 (10)</td>
<td>81 (17)</td>
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**Table 3** Prediction error (%) of propofol concentration and its absolute value obtained before and during surgery. Data are mean (SD)

<table>
<thead>
<tr>
<th>Prediction error (%)</th>
<th>Absolute prediction error (%)</th>
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<tbody>
<tr>
<td>Before surgery (n=49)</td>
<td></td>
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<tr>
<td>32 (16)</td>
<td>32 (15)</td>
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<tr>
<td>During surgery (n=19)</td>
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<td>25 (29)</td>
<td>34 (19)</td>
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this patient, Gepts’ pharmacokinetic model was used to control propofol concentrations. This lacked precision and caused abnormally high measured concentrations in one patient. Gepts’ pharmacokinetic model was obtained in young adults undergoing sedation, and may not be sufficiently accurate to predict surgical concentrations. Although the weight and age range of our patients was different from those for which the Marsh model was validated, we obtained a mean prediction error, and mean absolute values similar to those previously published. Marsh’s pharmacokinetic model fitted the present clinical purpose well, as suggested by the absence of movement during surgery and by the low mean prediction error of the model after induction as well as after prolonged infusion. Indeed, the prediction error of propofol remained stable during the whole procedure suggesting that the observed change in tcMEP was not a result of an error in predicted propofol concentration, but resulted from changes in spinal cord function. Therefore, the Marsh model is now used routinely in our institution for anaesthesia for scoliosis surgery with tcMEP because it allows deep anaesthesia, stable propofol concentrations whatever the duration of infusion, and precise determination of propofol effects on tcMEP.

In this study, greater propofol concentration reduced tcMEP amplitude in a dose-dependent manner, without affecting latency. In the clinical range of propofol concentrations, this effect is of moderate intensity, but may be severe when propofol is over dosed. This effect was observed after a delay to allow an equilibration of propofol between the plasma and effect-site compartments, indicated by the decrease in BIS values in response to propofol increase. These results are not affected by core temperature, $P_{\text{ET}}CO_2$ or blood pressure, because their values remained stable when the dose–effect relationship was obtained. Because noxious stimuli do not modify myogenic motor evoked potentials during a propofol-based anaesthesia, our results are not likely to have been affected by differences in the depth of analgesia. We found that it is possible to maintain anaesthesia with hypnotic doses of propofol (without nitrous oxide) and to record tcMEP adequately. Other authors have used propofol for anaesthesia maintenance and simultaneous MEP measurements. However, in
these studies, propofol was given at a constant infusion rate either alone, or to supplement a ketamine-based anaesthesia.\textsuperscript{5-7,9,14-16} In such studies, MEP during propofol anaesthesia were of similar amplitude to those with an opioid–nitrous oxide-based anaesthetic technique, but less than during ketamine–nitrous oxide anaesthesia.\textsuperscript{16} A dose–effect relationship was not investigated, and propofol was infused at a constant rate, which would have resulted in progressively increasing propofol concentrations, and a risk of decreasing MEP amplitudes. Indeed, doubling the propofol concentration from 0.7 mg litre\textsuperscript{−1} to 1.4 mg litre\textsuperscript{−1} may reduce MEP amplitude by 30–50%.\textsuperscript{15} We did not observe such a profound effect of doubling propofol concentration, perhaps because nitrous oxide was omitted. Nitrous oxide 40–60% given during propofol infusion reduces MEP amplitude by 50–70%,\textsuperscript{5,16,18} suggesting that nitrous oxide enhances the effects of propofol on the MEP. When nitrous oxide was combined with propofol, tcMEP amplitude was three times less than during ketamine–nitrous oxide anaesthesia.\textsuperscript{16}

Multipulse stimulation allows quantitative monitoring of MEP by transcranial electric stimulation during anaesthesia with propofol.\textsuperscript{16,17} The ease of obtaining tcMEP in the present study may also be related to the use of high-frequency multipulse stimulation. Stimulation of the spinal cord in this way can overcome the conduction block caused by propofol at the alpha-motoneurone, which comes either from supraspinal inhibition or from decreased motoneurone excitability.\textsuperscript{12} Multipulse stimulation simulates the physiological spinal I- and D-wave pattern and allows temporal summation of excitatory post-synaptic potentials. Multipulse stimulation creates additional D-waves that help to overcome the inhibition of cortical I-waves induced by propofol.\textsuperscript{5,16,18}

We found that tcMEP amplitudes were attenuated in a dose-dependent manner by increasing propofol concentrations, whereas their latencies remained unchanged. Large concentrations of propofol can suppress tcMEP recording. Thus, the effects of propofol on the tcMEP must be known before surgery to allow correct interpretation of changes in tcMEP. This can be done easily in current practice by limiting measurements to the clinical range for propofol, namely 2–4 mg litre\textsuperscript{−1}. Moreover, a combination of propofol and remifentanil without nitrous oxide or neuromuscular blocking agent can provide adequate anaesthesia and allows recording and interpretation of tcMEP. Thus a wake-up test was not used in most of the patients, except in one, in whom a spinal cord lesion was diagnosed by the disappearance of tcMEP and confirmed by the wake-up test.

References