SOME EFFECTS OF ISOFLURANE ON I WAVES OF THE MOTOR EVOKED POTENTIAL

R. G. HICKS, I. J. WOODFORTH, M. R. CRAWFORD, J. P. H. STEPHEN AND D. J. BURKE

SUMMARY

We have investigated the effects of isoflurane anaesthesia on the motor evoked potential recorded in the extradural space during corrective spinal surgery in 15 patients. Isoflurane was added to a nitrous oxide in oxygen mixture supplemented with fentanyl and a neuromuscular blocking agent. Isoflurane was administered to achieve end-tidal concentrations of 2%, 1% and 0% in all patients, and also of 1.5% and 0.5% in nine patients. Transcranial electrical stimulation of the motor cortex was used to elicit descending volleys in corticospinal axons (the motor evoked potential). With stimuli of 450-750 V and no isoflurane, multiple I waves were always seen following the D wave. In all patients the number of I waves decreased and individual I waves became smaller in amplitude the greater the isoflurane concentration, but there were only minor changes in the D wave. The greatest depressant effect on I waves occurred at an end-tidal concentration of 0.5%. Given that I waves are an index of synaptic transmission, anaesthetic-induced changes in I waves may provide a useful model for the neuronal events underlying anaesthesia-induced unconsciousness.

KEY WORDS

Simultaneous transcranial stimulation of the motor cortex and percutaneous stimulation of the tibial nerves allows a descending corticospinal volley (motor evoked potential, MEP) and ascending sensory volley (somatosensory evoked potential, SSEP) to appear as separate, identifiable potentials in extradural recordings from the spinal cord [1, 2]. We use this technique routinely to monitor spinal cord function during scoliosis surgery [2]. One advantage of this technique is that adequate anaesthesia and full neuromuscular block may be maintained. However, the level of anaesthesia must have some effect on the MEP given that it is a complex volley containing components that are generated trans-synaptically [3].

Transcranial electrical stimulation of the human motor cortex evokes a series of descending waves in the corticospinal tract [1, 3–7]. The waves of lowest threshold and shortest latency (D waves) are produced by direct activation of corticospinal neurones or their axons, and the later waves (I waves), with higher thresholds and longer latencies, result mostly from synaptic activation of corticospinal neurones because of stimulation of cortical interneurones [3, 5, 6, 8, 9]. This combination of D and I waves comprises the motor evoked potential as seen in extradural recordings from the spinal cord [1, 7], although the MEP may consist of only a D wave, particularly when low stimulus intensities are used (as in fig. 1).

There is little in the literature on the effects of volatile anaesthetic agents on the motor evoked potential recorded from electrodes in the extradural space in response to transcranial electrical stimulation of the motor cortex. This may be because it is more usual to record the MEP as a compound muscle action potential (CMAP) rather than as a spinal cord volley. Anaesthetic-induced changes in this transcranially-evoked CMAP have been well documented [10–18].

When recording the MEP as a CMAP there are two possible sites for an anaesthetic-induced change: at the motor cortex and at the corticospinal synapses with anterior horn cells. In the former, there would be a change in the descending corticospinal volley recorded using extradural electrodes; in the latter there would be no such change. Loughnan and colleagues [19] have reported that halothane and propofol do not alter the corticospinal volley in extradural recordings, but these findings did not accord with our anecdotal experience.

Therefore, we investigated patients undergoing scoliosis surgery with routine combined motor and somatosensory evoked potential monitoring, in an attempt to document whether the concentration of inhaled anaesthetic affects the corticospinal volleys evoked by transcranial electrical stimulation.

ISOFLURANE AND MOTOR EVOKED POTENTIALS

MEP SSEP

Low thoracic

FIG. 1. Normal MEP and SSEP recorded during scoliosis surgery. The stimulus to the motor cortex and that to the peripheral nerve were delivered simultaneously, at the onset of the traces. Because of the long peripheral conduction time, the ascending sensory volley reaches the low thoracic electrode after the descending motor volley. Hence, the descending motor volley appears in both recordings to the left of the dotted line and the ascending sensory volley to the right of this line. Note that in this study the D wave consists of a single wave. In this figure, and in figure 2, the recordings are duplicate averages of the MEP and SSEP recorded from bipolar extradural electrodes placed in T1-2 (high thoracic) and T12-L1 (low thoracic) intravertebral spaces. The polarity of the motor volley is inverted in the bipolar recording in this figure and in figure 2 (female, aged 16 yr).

PATIENTS AND METHODS

Fifteen children and adolescents (12 female), aged 10-17 yr (mean 13.7 yr) were admitted for surgical correction of scoliosis. None had clinical evidence of central nervous system dysfunction although three patients suffered from Duchenne muscular dystrophy. Cotrel-Dubousset instrumentation was used for correction in 12 patients, Luque rods in one and Cotrel-Dubousset rods with sublaminar wires in two patients. Written informed consent, as approved by the Human Studies Committee, was obtained from the patients and parents or relatives, as appropriate, for the surgical, anaesthetic and neurophysiological procedures.

Anaesthesia

After routine premedication, usually with papaveretum 0.4 mg kg⁻¹, hyoscine 0.08 mg kg⁻¹ and droperidol 0.1 mg kg⁻¹, anaesthesia was induced with thiopentone 5 mg kg⁻¹, and tracheal intubation facilitated with vecuronium or pancuronium 0.1 mg kg⁻¹. The lungs were ventilated with 70% nitrous oxide in oxygen and anaesthesia supplemented with fentanyl. A cannula was inserted into a radial artery to monitor arterial pressure and two peripheral venous cannulae were inserted for fluid infusion and sodium nitroprusside administration. Temperature probes were placed in the nasopharyngeal space and in the external auditory canal and connected to electronic thermometers (La Barge Mon-a-Therm 6000); temperature was maintained within 0.5 °C in the range 33-35 °C. The inspired isoflurane concentration was changed from the initial value to give stable end-tidal concentrations of 2%, 1% and 0%. In nine patients MEP measurements were obtained also with end-tidal concentrations of 1.5% and 0.5% isoflurane.

Monitoring

After each patient was positioned prone on the operating table, spiral needle electrodes were placed subdermally in the scalp at the vertex and 7 cm laterally. Previous experience [2] had confirmed that this was the optimal electrode configuration for the production of D and I waves during routine monitoring with vertex-anode to lateral-cathode polarity. These electrodes were connected to an isolated cortical stimulator with a low output impedance (Digitimer D180A) capable of producing a capacitatively coupled discharge of up to 1500 V. The output was scaled by a continuous turn potentiometer into 10 equal divisions, each representing 150 V. In calibration tests there was a linear relationship between the scale and the rated output. During operation the transcranial stimulus was delivered approximately once every 3 s.

The monitoring procedure involved simultaneous recording of descending corticospinal volleys (produced by transtranial stimulation of the motor cortex) and ascending somatosensory volleys (produced by percutaneous stimulation of the tibial nerves in the popliteal fossae), as described previously [2] (see fig. 1). The somatosensory stimulus was supramaximal for the ascending volley and remained constant throughout the operation. It was triggered simultaneously with the cortical stimulus (i.e., at a rate of about once every 3 s). Because of peripheral conduction times from popliteal fossa to cord, the ascending sensory volley reached the low
RESULTS

Corticospinal volleys were recorded while the end-tidal concentration of isoflurane was altered; the MEP was measured at 2%, 1% and 0% concentrations in all 15 patients and additionally at 1.5% or 0.5% in nine patients. At stimulus levels of 450–750 V and no isoflurane, multiple I waves were always seen following the D wave. Figure 2 shows a bifid D wave followed by seven I waves. In this patient 13 and 15 are the I waves of greatest amplitude: 14 is the dominant I wave. The mean amplitude of 14 was 10.7 ms (range 9.3–9.6 ms); and 19 10.7 ms (10.4–11 ms).

The total number of I waves recorded with 2% isoflurane in the 15 patients was 31; this increased to 42 with 1% isoflurane and increased to 74 when the isoflurane was discontinued. The longest latency I wave was 14 (mean latency 5 ms) with 2% isoflurane, 15 (mean latency 6.1 ms) with 1% isoflurane, and 19 (mean latency 10.7 ms) with no isoflurane. The I wave incidence for each concentration is shown in figure 3. Mean I wave amplitudes are shown in figure 4 and it may be seen that with no isoflurane 13 was the dominant I wave. The mean amplitude of 14 was slightly less. With 1% and 2% isoflurane, 12 had the greatest mean amplitude.

The amplitudes of the individual I waves were summed for each patient to quantify the overall effect of isoflurane on I wave generation. The total I wave amplitude and total number of I waves for 2%, 1% and 0% end-tidal isoflurane concentrations are shown in figure 5. Using a paired t test, there were significant differences in total I wave amplitude between 2% and 1% isoflurane (P = 0.009), be-
ISOFLURANE AND MOTOR EVOKED POTENTIALS

FIG. 3. Mean data (n = 15) indicating the occurrence of individual I waves at different isoflurane concentrations. With 0% isoflurane (■), all 15 patients had 11-14, but 19 was seen in only two patients. The change in number of I waves was greater between 0% and 1% isoflurane (□) than between 1% and 2% isoflurane (■).

FIG. 4. Mean (SE) amplitude of each I wave for the different end-tidal concentrations of isoflurane. There were no I waves later than 14 with 2% isoflurane (■) and none after 15 with 1% isoflurane (□) (■ = 0% isoflurane).

tween 2% and 0% (P = 0.0012) and between 1% and 0% isoflurane (P = 0.0016). As indicated in figure 5, there was a proportionately greater effect of isoflurane on amplitude than on number. In order to define more accurately the critical isoflurane concentration, recordings were made in nine of the 15 patients at concentrations of 0.5%, 1.5%, or both, in addition to those at 2%, 1% and 0%. Total I wave amplitude for each patient at these concentrations is shown in figure 6.
Fig. 5. Mean (SE) overall depressant effect of isoflurane on I wave generation. For each patient the amplitudes (■) of individual I waves were summed and the number (□) of I waves noted (n = 15).

Fig. 6. Determination of the critical end-tidal isoflurane concentration. Individual data points for nine patients in whom end-tidal concentrations of 1.5% and 0.5% were used in addition to 2%, 1% or 0%. There was little additional depressant effect when the isoflurane concentration was greater than 1%. The thick line shows the mean curve for the nine patients.

DISCUSSION

Previous studies have demonstrated anaesthetic-induced changes in compound muscle action potentials (CMAP) evoked by transcranial electrical stimulation of the motor cortex. Calancie and colleagues found that the addition of isoflurane to the anaesthetic caused marked attenuation of CMAP amplitudes in all patients within 5 min of its application, without affecting neuromuscular transmission, as judged by direct peripheral nerve stimulation [10]. Two other studies measured
CMAP evoked by transcranial electrical stimulation in rats and found that isoflurane caused a progressive increase in latency and decrease in size of the CMAP [11, 12]. Nitrous oxide was shown also to reduce markedly the CMAP recorded in response to single transcranial electrical stimuli to the motor cortex in healthy human volunteers and in patients undergoing neurosurgery for closed head injuries [13]. Zentner and Ebner [14] found that nitrous oxide could abolish completely the CMAP in rats produced by motor cortex or extradural spinal cord stimulation. Other studies [15, 16] have indicated that halothane and barbiturates also alter the MEP. Katayama and colleagues [17] found that the D wave was resistant to anaesthesia and unaffected by neuromuscular blockers, but stated that negative waves following the D wave (I waves) were vulnerable to anaesthesia, a finding confirmed by Thompson and colleagues [18].

Others have seen marked attenuation of the CMAP with nitrous oxide anaesthesia [13], and it is likely that this effect was on the spinal motoneurone pool rather than the corticospinal volley [14]. However, in the present study, the administration of 70% nitrous oxide remained unaltered throughout the operation. Fentanyl was administered intermittently with doses increased at times of isoflurane withdrawal. It is unlikely that fentanyl can cause the increase in I waves and thus the changes are attributed to isoflurane withdrawal. In addition, Loughnan and co-workers [19] observed infrequent small I waves when using halothane or propofol in addition to nitrous oxide. These observations suggest that depression of I waves may represent a fundamental difference in effect between an anaesthetic agent which primarily produces unconsciousness, such as the volatile agents or propofol, and one which has a large analgesic component to its action, such as nitrous oxide or an opioid.

In a review of anaesthetic agents at synapses, Richards [20] concluded that there was no effect of anaesthetics on synaptic transmission. However, Jessop and colleagues [21] showed that impairment of consciousness with nitrous oxide was associated with depression of long latency waves in the auditory evoked response, while early waves were well preserved. Kirschfeld and Baier-Rogowski [22] showed that large neurones, with long dendrites, axonal arborizations, or both, were most sensitive to the influence of anaesthetics. In the vertebrate nervous system, exceptionally large reticular neurones form widespread networks and some of these appear to play a role in altering the state of consciousness and alertness. It may have been the size of these neurones with their many synaptic connections that made them especially sensitive to anaesthetics. Work in human subjects has shown that amnesia is produced more reliably by isoflurane than nitrous oxide at equipotent subanaesthetic concentrations [23]. Also, peak velocity of saccadic eye movements, an indicator of brainstem reticular function, is depressed more by isoflurane than equipotent concentrations of nitrous oxide [24].

These findings suggest that cortically evoked I waves, which occur with long latencies and are depressed by isoflurane, halothane and propofol more than by nitrous oxide or opioids may be used as a measure of synaptic transmission, thereby providing indirect insight into anaesthesia-induced unconsciousness.

Frei and co-workers [25] showed that end-tidal concentration measurements of isoflurane may underestimate the arterial saturation during isoflurane uptake and overestimate during elimination. However, these errors are more likely to be seen in elderly and obese patients and those with a reduced vital capacity and abnormal carbon dioxide arterial: expired concentration ratios. All the patients in our group were juveniles, with height:weight ratios within the normal range for age, and adequate vital capacity and gas exchange. In addition, the I wave changes described are essentially qualitative and were seen consistently even with low concentrations of isoflurane.

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REFERENCES


