Effect of propofol anaesthesia on the event-related potential mismatch negativity and the auditory-evoked potential N1

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Background. Studies on the effects of anaesthesia on event-related potentials and long latency auditory-evoked potentials (AEP) are sparse. Both provide information on cortical processing and may have potential as monitors of awareness. We studied the effect of propofol on the event-related potential mismatch negativity (MMN) and the long-latency AEP N1.

Methods. Twenty-one patients received 1 μg ml⁻¹ stepped increases in the target concentration of propofol using Diprifusor™ until a maximum of 6 μg ml⁻¹ was achieved or the patient had lost consciousness. Neurophysiological responses (MMN and N1) and the patients’ level of consciousness were recorded before the administration of propofol and at a target effector site concentration of propofol of 1, 2, 3, 4, and 6 μg ml⁻¹. Grand average evoked potentials were computed at baseline, before the administration of propofol (A); at the highest propofol concentration at which each patient was responsive (B); and at the concentration of propofol at which the patient became unconscious (C).

Results. Patients lost consciousness at different target concentrations of propofol, all being unresponsive by 4 μg ml⁻¹. The response to the deviant stimuli used to elicit duration-shift MMN was significantly more negative than to the standard stimuli at A (mean difference 2.58 μV, P=0.0011) but this difference was virtually abolished at point B, before the patients lost consciousness (mean difference 0.63 μV, P=ns). The amplitude of N1 evoked by standard stimuli was negative compared with electrical baseline at both point A (mean amplitude −3.81 μV, P<0.001) and at point B (mean amplitude −2.2 μV, P=0.002), but was no longer significantly different to baseline at point C (mean amplitude 0.51 μV, P=ns). The change in the mean amplitude of N1 from last awake (point B) to first unconscious (point C) was also significant (mean difference in amplitude 1.69 μV, P=0.02).

Conclusions. MMN is unlikely to be a clinically useful tool to detect awareness in surgical patients. In contrast, the loss of N1 may identify the transition from consciousness to unconsciousness and deserves further study.

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Effect of propofol on MMN and N1

Patients and methods

We studied 21 ASA I or II unpremedicated patients aged between 31 and 65 yr who were to undergo elective general surgical procedures under general anaesthesia. The hospital ethics committee approved the study, and written informed consent was obtained from each patient. All subjects were free from neurological or otological disease. The study was carried out in the anaesthetic room before the start of the surgical procedure. The patients’ arterial pressure, electrocardiogram, and peripheral oxygen saturation were monitored non-invasively. All patients received supplemental oxygen via a Hudson facemask at 4 litre min\textsuperscript{-1}.

The only drug administered for the duration of this study was propofol which was infused using a target-controlled infusion (TCI) system (Diprifusor\textsuperscript{TM} TCI, Zeneca Ltd, Cheshire, UK).\textsuperscript{12} The TCI system consists of a microprocessor-driven infusion pump that adjusts the infusion rate to achieve the desired target concentration of propofol as predicted by a three-compartment pharmacokinetic model.\textsuperscript{13} The model assumes immediate mixing in blood and takes no account of the delay required to achieve drug equilibration in the brain. Thus, a delay occurs between the time the TCI system indicates that a target concentration has been achieved and the maximum pharmacodynamic effect. Using a computer simulation model of the pharmacokinetic variables, it was assumed that 5 min would be sufficient to achieve steady-state conditions between the blood and effector site compartments, and that after this period there would be minimal change in the clinical effect of the propofol.

After a baseline recording of the EEG and MMN had been made, the TCI pump was started and set to achieve a target blood concentration of 1 $\mu$g ml\textsuperscript{-1} and, after a period of 5 min for equilibration, EEG and MMN recordings were repeated. The level of consciousness was assessed at the end of the 5-min equilibration period and again after the recordings had been taken. The patients were deemed to be unconscious and unaware if they no longer obeyed commands and the eyelash reflex was absent. The procedure of infusion, equilibration, neurophysiological data collection, and assessment of consciousness was repeated at target blood concentrations of propofol of 2, 3, 4, and $6$ $\mu$g ml\textsuperscript{-1}. The study was stopped if the mean arterial pressure was reduced by more than 20% of the baseline value. Only when all the required recordings had been made were further drugs administered and the airway manipulated to allow the planned surgical procedure to begin.

Neurophysiology

The EEG was recorded from 10 scalp electrodes (F3, Fz, F4, C3, C4, A1, A2, P3, P4, and Cz) referred to a nose electrode, with a time constant of 1.2 s and a high-frequency filter at 70 Hz. The recordings were subsequently referenced to averaged mastoids ((A1+A2)/2). The signals were amplified
by a Nihon Koden 7300F EEG machine and digitized at 1000 Hz and 12-bit resolution. Responses to deviants and standards were averaged separately over epochs of 512 ms until responses to 32 deviants had been collected. Frequency-shift MMN was evoked using 990 Hz standard tones and 500 Hz deviants, each with a duration of 84 ms. Duration-shift MMN was evoked with 700 Hz tones, the standards lasting 75 ms and deviants 25 ms. Fifteen per cent of stimuli were deviants, 85% standards. All stimuli were presented at an intensity of 60 dB nl and with an inter-stimulus interval of 750 ms.

To observe the neurophysiological changes associated with the transition from consciousness to unconsciousness we calculated grand averages of the N1 and MMN responses (duration-shift and frequency-shift) in each patient at the following times:

1. A, baseline, before administration of propofol;
2. B, at the target concentration of propofol each patient was last conscious;
3. C, at the target concentration at which they were first unconscious.

**Statistical methods**

MMN corresponds to a period of greater negativity in the response to the deviant than the standard stimuli in the period following N1. To assess whether MMN was reliably present, the difference in the mean voltage of the responses to standards and deviants was assessed using paired Student’s t-tests. The period for analysis was chosen by inspection of the grand average responses recorded before the administration of propofol, which is at stage A. This showed that frequency-shift MMN was present during the period 100–250 ms after the stimulus and 140–250 ms in the case of duration-shift MMN. The onset of duration-shift MMN is later than that of frequency-shift MMN because detection of the deviant cannot begin until the (longer) tone has ended.

To determine whether the amplitude of N1 itself differed significantly from electrical baseline, the mean voltage of the response to standards in the period 90–135 ms after the stimulus was assessed using paired Student’s t-tests. The period was selected because it spans the peak of N1 in the grand average recorded before the administration of propofol.

**Results**

**Propofol dose and level of consciousness**

Patients lost consciousness at different target concentrations of propofol. Eight patients became unresponsive for the first time at 2 μg ml⁻¹, 11 at 3 μg ml⁻¹, and two at 4 μg ml⁻¹. In no patient was there a change in level of consciousness between the end of the equilibration period and the next increase in the dose of propofol. Thus, the target blood concentration of propofol did not accurately predict the point at which consciousness was lost.

**MMN**

The changes in duration-shift MMN recorded from electrode Fz with respect to mastoids at times A, B, and C are shown in Figure 1. In the baseline recording, before the administration of propofol, the response to the deviants was significantly more negative than that to standards (mean difference=2.58 μV; standard error (SE) of the difference 0.68 μV; P=0.0011). At the target concentration of propofol at which the subjects were last aware, duration-shift MMN was already virtually abolished, that is its amplitude was no longer significantly different from zero (0.63 μV; SE=0.64 μV; P=ns). Once the subjects became unconscious, the response to deviants became more positive than that to standards though the difference did not reach significance. The amplitude of the MMN when the subjects were last aware did not differ significantly from its amplitude when they were first unconscious (mean difference 2.1 μV; SE=1.11; P=ns).

Frequency-shift evoked a MMN, which, as expected, began slightly earlier than that to duration-shift. Figure 2 shows the MMN to frequency-shift recorded from electrode Fz with respect to mastoids at three levels of consciousness. In the baseline recording, the response to the deviants was significantly more negative than that to the standards (mean difference=2.31 μV; SE=0.73 μV; P=0.005). Frequency-shift evoked a MMN that was still present in the last recording made while the subjects were last conscious (mean difference=1.38 μV; SE=0.56 μV; P=0.02). The response to the deviants remained more negative than that to standards after loss of consciousness but the difference was no longer significant. The variance in the amplitude of the MMN increased considerably with the onset of unconsciousness. Although its amplitude was lower than when the subjects were last conscious, the difference between the two conditions was not significant (mean difference=0.84 μV; SE=3.11; P=ns).

**N1**

N1 is the peak in the response to the standard tones. For example, the 700 Hz 75 ms tones, used as standards to evoke the duration-shift MMN, evoke an N1 potential that has a latency of approximately 110 ms (Fig. 3). In the baseline recording, N1 had a mean amplitude of ~3.81 μV (significantly above baseline: SE=0.54 μV; P<0.0001) in the latency window 90–135 ms. Figure 3 also shows a systematic decrease in the mean amplitude of N1 with increasing target blood concentrations of propofol. The amplitude of N1 was still negative with respect to baseline at 2 μg ml⁻¹ (1.5 μV; SE=0.69 μV; P=0.044) but the trace became significantly more positive than baseline during the same period at 3 μg ml⁻¹.
Effect of propofol on MMN and N1

Fig 1 The mean amplitude of duration-shift MMN 140–250 ms after the stimuli at different levels of consciousness. (Left) Grand average waveforms. The thin lines are responses to standard stimuli, thick lines responses to deviant stimuli. (Right) Mean amplitude of MMN with SE. A=at baseline, B=at the highest target concentration at which patients were last conscious, and C=at target concentration at which consciousness was first lost. *Responses to deviant stimuli significantly more negative than responses to standards.

Fig 2 The mean amplitude of frequency-shift MMN 100–250 ms after the stimuli at different levels of consciousness. Caption as Figure 1.

The mean amplitude of N1 at the highest concentration of propofol at which subjects were still conscious fell to −2.2 μV (Fig. 4) but this remained significantly above the electrical baseline (SE=0.65 μV; P=0.002). Once subjects were unconscious, the mean amplitude dropped to −0.51 μV, a value not significantly different from zero (SE=0.42 μV,
The change in the mean amplitude of N1 from last awake to first unconscious was significant (mean difference 1.69 μV; SE=0.50 μV; P=0.02).

The N1, in response to the 900 Hz tones, used as standards to evoke the frequency-shift MMN showed similar changes in mean amplitude with the level of consciousness. The mean amplitude of N1 at baseline was −4.3 μV in the period between 90 and 135 ms after the stimulus. Although it was reduced to −1.8 μV at the concentration of propofol when patients were last conscious, this was still significantly different from zero (SE=0.52 μV; P=0.003). Once consciousness was lost, the mean amplitude of the signal in the 90–135 ms window became positive at +1.1 μV but not significantly different.
from zero ($t=1.97, P=ns$). The variance in the amplitude of N1 did not increase during the same period as it did for MMN. The change in N1 amplitude from last awake to unconsciousness was significant (mean difference=$2.9 \mu V$; se=$0.71 \mu V, P=0.001$).

### Discussion

In this study we showed that both duration-shift and frequency-shift MMN were abolished by concentrations of propofol insufficient to produce unconsciousness. There were several patients in whom a clear MMN could not be elicited despite them being conscious and obeying commands. The variability of the frequency-shift MMN waveform after loss of consciousness would make it difficult to determine if it is present or absent in individual patients. Though the variability of the waveforms was somewhat less in the response to duration-shift, the MMN evoked by this form of stimulation was abolished before consciousness was lost. MMN, as recorded in this investigation, does not appear to discriminate the level of consciousness as we hypothesized on the basis of its role in cognitive processing. No tests of implicit or explicit learning or memory were used in this study, but it has been repeatedly documented that patients who are lightly anaesthetized can obey commands yet have no explicit memory of the event.14 15 If MMN is representative of short-term auditory echoic memory, then one could reasonably expect it to be present if explicit memory is being laid down. It is possible that the concentration of propofol at which MMN disappears is that at which the ability to lay down explicit or implicit auditory memory is lost, as opposed to that at which consciousness is lost. While the relationship between MMN and the formation of long-term memory has not been studied, the disappearance of MMN before loss of consciousness would be in accord with the dissociation between awareness and the ability to establish memories. Clearly this hypothesis would require further study.

The technical problems in recording MMN in individual patients also need to be addressed. Several factors contribute to the variability in the MMN responses. To evoke MMN it is necessary to use deviant stimuli that are, by definition, relatively infrequent. If recordings are to be clinically useful they must be made in the shortest possible time to enable changing levels of awareness to be detected. Almost 3 min were required to accumulate 32 epochs into the average response to deviants. An average containing so few responses may still be affected by noise induced from equipment in the theatre environment and the increases in amplitude of the background EEG as anaesthesia is induced. Increasing the number of responses to deviant stimuli would allow better resolution of the MMN response but at the cost of increasing the time required between recordings to a clinically unacceptable extent. Furthermore, since this study began, there have been preliminary reports of test–retest variation in serial recordings of MMN.16 17 These indicate that MMN may occasionally be unrecordable even in awake, unanaesthetized subjects. Although the factors responsible for this have not been determined, the finding casts further doubt on the value of MMN as a monitor of depth of anaesthesia.

In contrast, N1 evoked by the standard stimuli was less vulnerable to these sources of variance because many more responses were included in the average (approximately 200). This component stayed significantly above baseline while the patients remained conscious with both the 990 Hz 84 ms (used to evoke frequency-shift MMN) and the 700 Hz 75 ms standard tone bursts (used for duration-shift MMN). Once consciousness was lost, the waveform evoked by the 700 Hz tones fell to baseline in the period occupied previously by the N1 and became positive in response to 900 Hz tones. This is in keeping with the findings of previous reports of the effect of anaesthesia on N1. However, in these studies the induction of anaesthesia was by a rapid bolus of i.v. anaesthetic agent and the transition period from consciousness to unconsciousness was not studied in detail.18–20 In the present study, slowly increasing the depth of anaesthesia using the TCI system enabled us to see how N1 varied with predicted blood propofol concentration and the level of consciousness.

It may be argued that a longer period of equilibration than that chosen for this study is required to achieve a steady-state concentration of propofol at the effector site compartment.21 Therefore, it is possible that the concentration of propofol may have continued to increase from the end of the equilibration period to the end of data collection and may have had some effect on the neurophysiological variables being measured. While this is possible, the effects on our results should be minimal for two reasons. First, as we were using only 3- to 4-min epochs of data and the sequence of recordings was the same at each concentration of propofol, then the effect should have been consistent on each of the variables measured. Secondly, and more importantly, there was no change in the level of consciousness between the end of the equilibration period and the end of data collection in any patient. The study was primarily concerned with neurophysiological changes occurring at the transition from consciousness to unconsciousness, and not the correlation of neurophysiological variables to the predicted plasma concentration of anaesthetic agent. However, in the light of our findings it would be prudent if in future studies the time period for equilibration were increased and the incremental increase in the target concentration of propofol reduced to 0.2 or 0.5 $\mu g$ ml$^{-1}$ increments, particularly in the range where consciousness is lost, that is 2–4 $\mu g$ ml$^{-1}$.

The mean amplitude of N1 was a more sensitive predictor of the transition from consciousness to unconsciousness than was the predicted blood concentration of propofol. This is not surprising given the inter-individual pharmacokinetic and haemodynamic variability that will markedly affect each patient’s response to propofol and the fact that the
Diprifusor™ system has been shown to have a median performance error of 16%, even if allowed to equilibrate. 22 The later part of these waveforms becomes increasingly positive with reducing levels of consciousness. This phenomenon can be observed in the recordings of long latency event-related potentials published by previous investigators. 20,23 Although the waveforms are different from those which occur during normal consciousness, they indicate that some form of stimulus-related activity is still taking place in the cerebral cortex at these levels of anaesthesia. We hope to investigate the reproducibility and significance of this phenomenon in future studies.

Our study may be criticized for studying mean values as opposed to individual patient data. The study was designed to investigate the effect of loss of consciousness on the selected neurophysiological variables recorded and to that end multiple variables were studied for short periods only and grand averages compared. As we believe that in N1 we have identified a possibly useful neurophysiological marker of the transition from consciousness to unconsciousness, future studies of this variable should collect data over longer periods and compare changes in individual patients.

In conclusion, we have shown that the event-related potential MMN is not a robust measure of loss of consciousness and have postulated that it may represent the loss of ability to lay down auditory memory. We also demonstrated that the disappearance of the LLAEP N1 identifies the transition from consciousness to unconsciousness and warrants further investigation of its suitability of a monitor of depth of anaesthesia.

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