Mid-latency auditory evoked response during propofol and alfentanil anaesthesia

M. A. Tooley¹ ²*, C. L. Stapleton³, G. L. Greenslade³ and C. Prys-Roberts²

¹Medical Physics and Bioengineering and ²University Department of Anaesthesia, University of Bristol, Bristol, UK. ³Department of Anaesthesia, Frenchay Hospital, Bristol, UK

*Corresponding author: Department of Medical Physics, Bristol General Hospital, Bristol BS1 6SY, UK
E-mail: mark.a.tooley@bris.ac.uk

Background. Propofol has been shown to affect the mid-latency auditory evoked response (MLAER) in a dose-dependant manner. Few studies have investigated the addition of alfentanil. Myogenic responses, such as the post-auricular responses (PAR), can confound the MLAER but there has been little investigation as to which electrode site reduces this interference.

Methods. We studied the MLAER in 27 women. They received an infusion of alfentanil 15 µg kg⁻¹ h⁻¹, followed by either a high or low infusion regimen of propofol (final infusion rates 6 and 3 mg kg⁻¹ h⁻¹). We compared the results with those of our study using propofol alone. We collected the data from two electrode sites: vertex–inion and vertex–mastoid. We evaluated the occurrence of the PAR and the shape of the MLAER at each electrode site.

Results. The infusion rate of propofol associated with loss of the eyelash response in 50% of subjects was 3.3 mg kg⁻¹ h⁻¹. This was significantly lower than using propofol alone (5.8 mg kg⁻¹ h⁻¹). Nb latency was the best MLAER discriminator of unconsciousness (sensitivity 94%, specificity 88%), with a threshold of 46 ms (propofol alone was 53 ms). The addition of alfentanil did not alter the relationship between propofol infusion rate and MLAER. The vertex–inion electrode site gave the best protection against PAR in awake subjects (P=0.0003), and after 30 min of propofol infusion (P=0.06). The magnitude of the MLAER obtained from the vertex–mastoid electrodes was larger than from the other site, although the increase was not consistent throughout the waveform (brain stem 100%, Nb 14%).

Conclusions. Addition of alfentanil lowers the propofol infusion rate required to produce unconsciousness and the Nb latency that predicts it. The better of the two sites to reduce the incidence of PAR is the vertex–inion electrode site.

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The auditory evoked response (AER) is known to be affected by anaesthetic agents. The mid-latency auditory evoked response (MLAER) is more reliably altered by i.v.¹ ² and inhalation agents ³ ⁴ than other latencies (brain stem and late cortical). Previous work has shown a dose-dependent reduction in both amplitude and frequency content within this range. ⁵ This correlates with other measures of adequacy of anaesthesia.¹

We have examined previously the dose–response relationship of propofol as a single agent on the MLAER, in the absence of surgical stimulation.¹ In this paper, we investigate the effect of the addition of alfentanil in a similar controlled manner. We selected two infusion schemes of propofol that we predicted from the previous study would result in two distinct levels of sedation or anaesthesia—ideally one leaving the patient awake and the other the patient anaesthetized. We also found from this previous work that at least 20 min of propofol infusion was required before stable anaesthesia occurred. To obtain reliable responses, the MLAER was therefore recorded at 35 min.
Myogenic responses to the auditory stimulus, especially the
post-auricular response (PAR), can be many times larger
than the MLAER and can obscure it, making analysis
impossible. We therefore wanted to compare the MLAER
obtained from two different electrode sites and see if this
affected either the shape of the MLAER or the prevalence of
the PAR.

Patients and methods
We obtained approval for the study from the United Bristol
Healthcare Trust Research Ethics Committee. All women
(ASA I and II) undergoing elective gynaecological surgery
on a particular surgeon’s weekly operating list were
approached. Exclusion criteria were clinical hearing deficit,
neurological dysfunction and treatment with any drugs
affecting the central nervous system. Twenty-seven women
gave informed consent and were enrolled into the study.

We attached two sets of bipolar silver-silver–chloride
electrodes to the patients’ heads in a conventional con-
figuration. One pair was placed on the vertex (positive) and 2
cm above the inion (occipital bone at the base of the skull);
the other was placed on the vertex and the mastoid. A
forehead electrode was used as a reference. The impedance
was ensured to be below 5 kΩ. We applied the electrodes on
the ward before bringing the patient to the operating theatre.

In the anaesthetic room, we sited an i.v. cannula and
began monitoring ECG, automatic non-invasive arterial
pressures and pulse oximetry. We recorded baseline
 MLAER when each patient was awake, relaxed, and with
their eyes closed.

At the beginning of the study (time zero), we gave each
patient a loading dose of alfentanil 15 μg kg⁻¹, followed by
an infusion of 15 μg kg⁻¹ h⁻¹. At 5 min, we started one of the
two propofol infusion schemes in alternate patients. Group
H (high-dose group) received a loading dose of 1 mg kg⁻¹
(given at 600 ml h⁻¹) followed by a stepped infusion of
10 mg kg⁻¹ h⁻¹ for 10 min, 8 mg kg⁻¹ h⁻¹ for 10 min, and a
final rate of 6 mg kg⁻¹ h⁻¹. Group L (low-dose group)
received exactly half the loading dose and infusion rates.
Automatic non-invasive arterial pressure, heart rate, eyelash
reflex, and response to the command ‘squeeze my hand’
were recorded at 5-min intervals from time zero. MLAER
was recorded at 35 min. Immediately afterwards, with-
drawal response to venepuncture was noted when blood was
taken for propofol assay.

The blood was collected in oxalate tubes and stored at
4°C. Propofol assay was carried out using high performance
liquid chromatography. At the end of the study, the patient
was taken into the operating theatre and anaesthesia and
surgery continued as planned.

MLAER processing
We used similar equipment to that in our previous study. A
personal computer was used to control two signal process-
ing microprocessors (CED 1401 plus, Cambridge Electronic
Design Ltd, Cambridge), one as a programmable auditory
stimulator and the other for data acquisition. The auditory
stimuli (rarefaction clicks of 0.5 ms duration) were
delivered via insert headphones at 80 dB above the normal
hearing threshold. Each set of recordings consisted of at
least 500 sweeps of electroencephalograph (EEG). Each
sweep of EEG data lasted 128 ms with the auditory stimulus
occurring 28 ms after the beginning of the sweep. This
would divide the sweep into two: a pre-stimulus interval of
28 ms (where there should be no response), then a MLAER
in the following 100 ms. The signals were recorded using
two high quality patient-isolated EEG amplifiers (CED
1902). The amplifiers had analogue second order high pass
and low pass filters set to 3 db points of 15 and 200 Hz,
respectively. Data acquisition software (SIGAVG,
Cambridge Electronic Design) controlled the acquisition
parameters: repetition rate of the auditory stimulus (5.9 Hz),
the duration of the sweep, and the sampling frequency of the
EEG signals (1 kHz). A monitor displayed the real-time
coherent average MLAER, and the sweeps were stored on
disk for off-line processing.

The off-line processing consisted of coherent averaging.
Before each sweep was added to the average, it had an
artefact rejection algorithm applied. If a sweep was deemed
to have gross artefacts (i.e. a non-physiological signal or
50 Hz) or not be representative of the background EEG, then
it was not included. The artefact removal was done semi-
automatically using custom designed signal processing
software (SPIKE 2 language, Cambridge Electronic
Design). Additionally, all sweeps were digitally filtered by
a 15 Hz high pass filter to remove low frequency EEG. To
gain confidence in the final average and of the filtering and
artefact removal process, additional recording of 500
sweeps were made with no auditory stimulus present. It
was expected that the average of the background EEG
would tend to zero. Also, the pre-stimulus waveform should
tend to zero. The final satisfactory estimates of the MLAER
were stored as separate files for feature extraction and
analysis.

Feature extraction from the MLAER
The simple features that were extracted consisted of the
amplitudes (measured from the preceding peak or trough)
and latencies (from the stimulus) to the peaks or troughs of
the conventionally labelled components of the MLAER (Na,
Pa, Nb). Also, the amplitude of the brain stem wave V (BS)
was obtained for analysis. These were all obtained manually
by applying cursors to the screen display of each satisfac-
tory estimate of the MLAER.

Two empirically devised composite measures of the
complete MLAER wave were also used. One was the best
composite measure found in our previous study, which is
the integral of the rectified smoothed differential of the wave
form between 20 and 70 ms (differential index). The other
measure used was the AER index, which is the rectified smoothed squared differential of the complete AER wave.

Statistical analysis
We used Student’s t-tests to compare ages, weights, and baseline arterial pressure in Groups L and H. We used one-way analysis of variance to examine the effect of the anaesthetic regimen on arterial pressure with time.

We examined the incidence of PAR on the MLAER and BS waveforms and compared the effect of electrode placement and propofol infusions. The PAR is a large and well-defined response, considerably larger than the MLAER, typically lasting from 10 ms until 30 ms, with a well-defined positive peak around 12 ms and a well-defined negative peak around 17 ms. The proportions were analysed using \( \chi^2 \) analysis. We also investigated the effect of electrode placement of the MLAER waveform by comparing the amplitude of the simple AER measures (BS, Pa, and Nb). Significance analysis was carried out by \( t \)-tests.

We examined the effect the two propofol infusion groups (L and H) had on the derived variables of the MLAER waveform and compared the differences by \( t \)-tests.

We examined the relationship of serum propofol concentration with final propofol infusion rate using regression analysis.

Relationships between infusion rate and blood concentration, and between the value of features extracted from the MLAER, were determined by non-linear curve fitting programmes (Sigma-Plot for Windows version 8, SPSS Inc.). Logistic regression (Stata version 6) analysis was used to determine MLAER descriptors of the patients’ response to eyelash and venepuncture responses. Probit analysis (Stata version 6, and Arcus Quickstat) was used to estimate the 50 and 95% probabilities of no response.

Results
There were no significant differences between the two groups in age, weight, height, or arterial pressure, either at baseline or after 30 min of the propofol infusion.

Sampling and editing of the MLAER
Results from four patients were not included in the study because their MLAER data were too contaminated with 50 Hz and diathermy interference. The non-stimuli averages also did not tend to zero. Eleven patients remained in Group L and 11 patients in Group H, all of whom had satisfactory...
signals and all their non-stimuli averages tended to zero (including the pre-stimuli). One patient was maintained on an infusion of alfentanil. Satisfactory estimates of the awake MLAER were obtained from only 13 patients, but MLAER estimates could be obtained from all 22 patients during the propofol infusions. The final estimates required a variable degree of editing to exclude artefacts from the final coherent average.

**Dose–concentration effects**

The relationship between final propofol infusion rate (I) and blood propofol concentration (PC), was described by the regression equation:

\[ PC = 0.68 \times I - 0.48, \quad R^2=0.55 \]

This is shown in Figure 1. The grey regression line represents previous data and is considered in the discussion.

**PAR and electrode site relationships**

Table 1 shows the influence of electrode site on the incidence of PAR. In the awake patient, the difference in the incidence between the electrode sites is significant \( (P=0.0003) \) using \( \chi^2 \) with Fisher’s exact test. After 30 min of infusion of propofol, the electrode site used for analysis is not significant \( (P=0.06) \). However, if we only consider PAR amplitudes >1 μV in the analysis (the average value of the

![Fig 2 MLAER waveforms from: (a) an awake, anaesthetic free patient, vertex–inion configuration; (b) a patient receiving propofol (Group L), still awake, vertex–inion site; (c) the same patient as (b) but using vertex–mastoid site, showing large PAR; (d) an anaesthetized patient (Group H), vertex–inion configuration.](image-url)
brainstem amplitude), then the difference between the electrode sites is significant ($P=0.02$).

An example of an MLAER (vertex–inion) from an awake, drug free subject, with no PAR is shown in Figure 2A. Figure 2B and C show waveforms obtained from each electrode configuration from an awake patient receiving propofol (Group L). Figure 2B is the vertex–inion and Figure 2C is the vertex–mastoid. Figure 2C shows clearly a large magnitude PAR (28 mV) but the other electrode site (Fig. 2B) does not show a PAR even though those waveforms are recorded at the same time. Figure 2D shows an MLAER (vertex–inion) from an anaesthetized patient (Group H).

Table 2 shows the influence of electrode site on the amplitudes of the various components of the MLAER and the BS. The MLAER and BS waves have a greater overall magnitude in the vertex–mastoid configuration as can be seen comparing the vertex–mastoid row (3) with the vertex–inion row (2). This increase is not consistent throughout the waveform and decreases as the latencies are increased (e.g. Nb). The electrode site however, does not affect latencies.

**Dose–MLAER relationships**

Table 3 compares the influence of the two infusion rates of propofol (Groups L and H) on MLAER-derived variables. The change in infusion rate changes the derived variables significantly, with the Pa amplitude and the differential-index showing the greatest change.

Figure 3 shows the regression graphs of Nb latency against final infusion rate of propofol (I). The regression equation is:

\[
\text{latency (ms)} = 40.3 + 2.04 \times I, \quad R^2 = 0.63
\]
This relationship is linear. The grey regression lines represent previous data.\textsuperscript{1}

Figure 4 shows the regression of Nb latency against blood concentration (BC) of propofol. The regression equation is:

\[
\text{latency (ms)} = 40 + 5.62 \times \text{BC} \pm 0.54 \times \text{BC}^2, \quad R^2 = 0.72
\]

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Dose–concentration and MLAER indices on responsiveness to stimuli

Table 4 shows the derived MLAER variables and their abilities to discriminate between awake and anaesthetized patients. The best discrimination variable was Nb latency in terms of its correctness, sensitivity, specificity, and the statistical fit. For comparison, blood concentration and final infusion rate of propofol are included in the table as discriminators. The final infusion rate provided perfect discrimination as all Group H patients were anaesthetized.

Table 5 shows the results of probit analysis. Venepuncture is not modelled here because under the influence of alfentanil, when the patients lost their eyelash reflex, none responded to venepuncture. Two patients responding to the eyelash reflex had no venepuncture response.

**Discussion**

In a previous study,\textsuperscript{1} we investigated the effects of various infusion rates of propofol alone in unpremedicated patients on the MLAER. In the present study, our aim was to determine how propofol changes the MLAER with and without an alfentanil infusion. This was done in a strictly controlled manner, without the potentially confounding effect of surgery. The data for this study were collected immediately after the data collection for the previous study was finished. The methods, study location, and equipment were the same. We wished to determine whether the addition of the opioid infusion decreased the propofol infusion rate required to induce loss of consciousness. We also wished to determine if the opioid had any effect on the indices obtained from the MLAER, which could be used to predict loss of consciousness, as defined by loss of the eyelash reflex.

We found that increasing the infusion rate of propofol produced measurable changes in the MLAER, with the differential index and Pa amplitude being the best discriminators. However, the best predictor of loss of consciousness was Nb latency with a threshold value of 44
ms. This is lower than in our previous study (Nb=53 ms) using propofol alone, but similar to Thornton’s study (44.5 ms) in which a nitrous oxide background was used. It would appear that combining propofol with opioids or other analgesics reduces the value of Nb latency which predicts loss of consciousness. This might explain the large variation in predictive threshold values quoted in the literature for different drug combinations, or different anaesthetic drugs (which have different analgesic properties). This would suggest that MLAER might not be so useful as an absolute monitor of awareness, only as a relative one. Using propofol as an example, one could set the threshold for Nb latency to predict consciousness at the value based on data for propofol alone but, when the analgesic (for example, alfentanil) is added the threshold will shift to a lower value. Consequently, the value set is more likely to indicate adequate anaesthesia, with a higher margin for error. However, in this situation more drug than necessary may be used, increasing the potential for adverse clinical effects.

Our data suggest that the Nb latency (and other derivatives of the MLAER) has a relationship with the anaesthetic dose and this does not change when the analgesic (alfentanil) is added. This is shown in Figure 3, which shows the regression line (with confidence intervals) of the current data drawn with the regression line of our previous data for propofol alone, drawn in grey. The equations of these two regression lines are almost identical:

- latency (ms)=40.3+2.04 dose, $R^2=0.63$ (propofol plus alfentanil)
- latency (ms)=39.5+2.37 dose, $R^2=0.86$ (propofol only)

Other researchers have agreed with the finding that the addition of alfentanil to propofol does not change the dose–response relationship of MLAER. However, they concluded that alfentanil does not change the point at which the MLAER predicts arousal, but we have found that it does, for example the Nb latency value for loss of consciousness decreases to 46 ms. Table 4 shows the comparison of the predictive thresholds of our two studies, with and without alfentanil. This shows, for example, a reduction of the value of Nb latency that predicts arousal when alfentanil is added.

We found that less propofol was required to induce unconsciousness when alfentanil was added, and this paralleled the lower Nb latency that predicted loss of consciousness. Table 5 includes the comparison of the probability of no response with blood concentration and final infusion rate of propofol for the two studies.

Dutton and colleagues compared propofol and desflurane and MLAER. Their Nb latency values with propofol were similar to ours. However, their Nb latency values obtained during desflurane anaesthesia were different. This is further evidence that the Nb latency (or MLAER) values that predict arousal are agent specific.

The relationship between final propofol infusion rate and blood concentration in both our studies is interesting. Figure 1 includes the regression lines (grey lines) from our previous data of propofol only, and therefore demonstrates the regression of propofol blood levels related to final infusion rate for the two sets of data. Comparing the two regression lines, and their confidence limits, it would appear that when alfentanil is added to propofol, the blood concentration for a given final infusion rate is higher. The propofol assays were done by the same personnel in the same laboratory for both studies, making it unlikely that this finding is a result of error in the assay. This phenomenon has been noted before. It is further demonstrated in the graphs of Nb latency against propofol blood concentrations from the two studies, shown in Figure 4. The propofol only regression lines are shown in grey. Each concentration value with alfentanil gives a lower Nb latency value than with the propofol alone. This is consistent with higher propofol blood values being present with alfentanil, as each concentration value represents a lower final infusion value, and hence Nb latency. It seems possible that a pharmacokinetic interaction between propofol and alfentanil has led to increased plasma propofol concentrations.

The second aim of our study was to investigate which is the best electrode site to use for MLAER measurement. Some researchers state that vertex–mastoid is the site to use, whilst others use the vertex–inion configuration. There is little consensus on this matter, although it seems agreed that the vertex site gives the best amplitude response. We were interested if the choice of site had any effect on the occurrence of the PAR and the magnitude and shape of the MLAER. This confounding post-auricular response occurred in 60% of our subjects, but was less likely to occur in the vertex–inion configuration ($P<0.05$).

Decision about electrode configuration should be made with the individual situation in mind. If the experimental circumstances are looking at anaesthesia and analgesia only, then the best configuration is probably the vertex–inion one. This site gives the best protection against PAR, but this configuration does suffer from reduced amplitude for the beginning of the signal—the brainstem and early waves. The amplitude of the Nb and later waves seem to be affected less. If the circumstances involve the use of a neuromuscular blocking agent, then the PAR will be less of a problem (as it is a myogenic response). The vertex–inion configuration could be used. The choice of electrode site becomes more critical if a variable derived from the MLAER is used for automatic control of anaesthesia, or if the signal is processed to give a single value signal index, without any reference to the underlying waveform. A myogenic response appearing, such as the PAR, could alter the index for the wrong reason. Electrode placement tends to be quicker on the mastoid site, but we have had no problems in fixing electrodes to the inion, even when some of our patients had very full heads of hair.

The processed values (for example differential index) we have looked at previously and in this study are not as consistently predictive as the Nb latency. However, the Nb latency is normally obtained by visual inspection and it is
very difficult to extract from a waveform automatically using a computer algorithm.\textsuperscript{15} Our differential value\textsuperscript{1} appears to be useful and indeed other researchers have proposed this approach.\textsuperscript{16} More recently, Kenny and colleagues\textsuperscript{9} proposed an altered version of this, using the square of the differential and using the full width of the signal. As this AER index does not filter out background EEG or brain stem AER, its lesser sensitivity and specificity are not surprising.

It is technically difficult to obtain the MLAER robustly. Awake, unpremedicated and sedated patients are the most challenging, as electromyographic (EMG) responses and PAR occur within the frequency pass band of interest and can be difficult to remove. Using the vertex–ion configuration can reduce this problem. We found that great care was needed to obtain confident estimates of the MLAER, and we had constantly to ensure that we were looking at MLAER, and not artefacts, by checking with the unstimulated signals and the signals collected pre-stimulus. Both of these unstimulated signals should produce a flat MLAER trace.

Proposed monitors that present a single number to represent the clinical state are attractive, but if this number is not accompanied by a measure of confidence, or an indicator showing the waveform shape, then it may be spurious. For example, if frontal electrodes are used, and the patient becomes more aroused, then frontal EMG can appear in the unprocessed signal. The averaging process may or may not translate these signals into high frequency components in the MLAER, but this process is likely to be unpredictable and inconsistent. The result of this would be an inaccurate, inappropriately high number. MLAER processing using coherent averaging requires a stable state of anaesthesia. Therefore, the MLAER is less useful when there are rapidly changing drug levels. There are techniques becoming available using single MLAER estimates, however, which are promising.\textsuperscript{16} Our work suggests that a monitor would have to have some knowledge of which drug or drug combination was being used and a reference table used to provide different thresholds for prediction. If the thresholds were to be based on the anaesthetic drug only studies, then this would provide maximum sensitivity, but lower specificity.

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