EFFECTS OF INCREASING DOSES OF ALFENTANIL, FENTANYL AND MORPHINE ON MID-LATENCY AUDITORY EVOKED POTENTIALS

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SUMMARY
We have studied dose-dependent effects of alfentanil, fentanyl and morphine on mid-latency auditory evoked potentials (MLAEP). Anaesthesia was induced with alfentanil 100 μg kg⁻¹ every 5 min to a total dose of 500 μg kg⁻¹ (group I, n = 10), fentanyl 10 μg kg⁻¹ every 7 min to a total dose of 50 μg kg⁻¹ (group II, n = 10) or morphine 1 mg kg⁻¹ for induction and 0.5 mg kg⁻¹ every 15 min to a total dose of 3 mg kg⁻¹ (group III, n = 10). MLAEP were recorded before and 3-15 min after every opioid dose on vertex (positive) and mastoids on both sides (negative). Latencies of the peaks V, Na, Pa, Nb, P1 (ms) and amplitudes Na/Pa, Pa/Nb and Nb/P1 (μV) were measured. Fast-Fourier transformation was used to calculate power spectra of the AEP. In the awake state, MLAEP had high peak-to-peak amplitudes and a periodic waveform. Power spectra indicated high energy in the 30-40 Hz frequency range. During general anaesthesia with increasing doses of alfentanil, fentanyl and morphine, the brainstem response V was stable. There was a marked increase only in latency and decrease in amplitude of P1. In contrast, for the early cortical potentials Na and Pa, only small increases in latencies and decreases in amplitudes were observed. After the largest doses of alfentanil (500 μg kg⁻¹), fentanyl (50 μg kg⁻¹) and morphine (3 mg kg⁻¹), Na, Pa and Nb showed a similar pattern as in awake patients. In the power spectra, high energy persisted in the 30-Hz frequency range. There were no dose-dependent effects of opioids on MLAEP and no differences between alfentanil, fentanyl and morphine could be found. (Br. J. Anaesth. 1993; 71: 622-628)

KEY WORDS

The process of transduction, transmission and processing of acoustic stimuli from the cochlea to the cortex can be monitored by the recording of auditory evoked potentials (AEP) [1]. Early components of the AEP (0-10 ms after stimulus) are generated mainly in the brainstem (brainstem auditory evoked potentials—BAEP) and represent the process of stimulus transduction [1]. The mid-latency auditory evoked potentials (MLAEP) occur 10-100 ms after stimulus presentation and are generated by different overlapping areas of the primary auditory cortex. They are the electrophysiological correlate of primary cortical processing of auditory stimuli [1-6]. Finally, late latency auditory evoked potentials (LLAEP) reflect neural activity of the association cortex 100-1000 ms after stimulus onset. They are influenced strongly by processes of stimulus evaluation and cognitive analysis.

The early evoked potentials, generated in the brainstem, remain almost stable under anaesthesia [7-9]. The late cortical components show a great variation of latencies and amplitudes in the awake state [1,10]. In contrast, mid-latency peaks of the AEP do not differ intra- and interindividually. Recordings of MLAEP therefore offer the opportunity to monitor auditory information processing in the primary auditory cortex during general anaesthesia.

Under general anaesthesia with volatile anaesthetics, MLAEP are suppressed dose-dependently [7,8,11], therefore MLAEP have been used to measure depth of anaesthesia and to indicate intra-operative awareness [11,12]. Opioids produce analgesia and sedation and are also used for induction and maintenance of general anaesthesia. Dose-dependent effects of opioids on MLAEP have not been studied previously. Because intraoperative awareness, and especially the perception of auditory stimuli, are observed occasionally under general anaesthesia with high-dose opioids, we have studied dose-dependent effects of alfentanil, fentanyl and morphine on MLAEP.

PATIENTS AND METHODS
Institutional Ethics Committee approval and informed consent were obtained to study 30 patients (40-70 yr, ASA II and III) undergoing elective...
AEP AND OPIOIDS

FIG. 1. Auditory evoked potential and its power spectrum of an awake patient. V belongs to the brainstem generated potentials (BAEP), which demonstrates that auditory stimuli were transduced correctly. Na, Pa, Nb and P1 (mid-latency auditory evoked potentials (MLAEP)) are generated in the primary auditory cortex of the temporal lobe and have a characteristic periodic waveform—the power spectrum has its maximal energy in the 30–40 Hz frequency range.

cardiac surgery. After oral premedication with flunitrazepam 1–2 mg 45–60 min before anaesthesia, continuous ECG recordings were commenced and a vein cannulated. The radial artery was cannulated for continuous arterial pressure measurement. Patients were then allocated randomly to one of three groups. Anaesthesia was induced and maintained in group I (n = 10) with alfentanil 100 µg kg\(^{-1}\) every 5 min to a total dose of 500 µg kg\(^{-1}\), in group II (n = 10) with fentanyl 10 µg kg\(^{-1}\) every 7 min to a total dose of 50 µg kg\(^{-1}\) and in group III (n = 10) with morphine 1 mg kg\(^{-1}\) for induction and 0.5 mg kg\(^{-1}\) every 15 min to a total dose of 3 mg kg\(^{-1}\).

After induction of general anaesthesia with the first opioid injection and loss of consciousness (no response to verbal commands, loss of eye lash reflex), the patient’s lungs were ventilated with 100% oxygen via a face mask. Pancuronium 0.1 mg kg\(^{-1}\) was given for neuromuscular block, the trachea was intubated and controlled ventilation with 100% oxygen commenced. Heart rate (ECG) and direct arterial pressure were recorded continuously and mean arterial pressure was maintained greater than 80 mm Hg. Body core temperature was measured by an oesophageal temperature probe and maintained > 34.5 °C using heated blankets and warmed infusions. A central venous catheter was placed via the internal jugular vein. Controlled ventilation was adjusted to maintain normocapnia (\(\text{PaCO}_2\) 4.6–5.9 kPa) and monitored by intermittent arterial blood-gas analysis.

The electrodiagnostic system Pathfinder I (Nicolet Instruments) was used for auditory stimulation, registration and analysis of evoked potentials. Rarefaction clicks of 0.1 ms duration and 70 dB greater than normal hearing level were presented binaurally with a stimulation frequency of 9.3 Hz using acoustically shielded earphones (TDH 39). For recording, silver electrodes were positioned at Cz and A1/A2 with Fpz as ground (according to the international 10–20 system). The impedance of all electrodes was maintained less than 0.5 kΩ. An epoch of 100 ms (bin width 0.2 ms) was bandpass filtered (1–1500 Hz) with an analog Butterworth-filter (roll-off 6 dB/Octave) and averaged across 1000 stimulus presentations. The recording procedure was controlled visually on a monitor, and an automatic artefact detector rejected signals greater than 96% of full scale. To guarantee reliability of the signal and correct transmission and transduction of the auditory stimuli, evoked potentials without a brainstem response (peak V) were rejected also.

Latencies of the peaks V, Na, Pa, Nb and P1 (ms) and amplitudes Na/Pa, Pa/Nb and Nb/P1 (µV) were measured. For frequency analysis, a Fast-Fourier Transformation was used to calculate power spectra of the AEP. For each situation, AEP of each individual patient and an interindividual grand average calculated from the individual AEP of all patients in each group were analysed. Auditory evoked potentials were recorded awake and 3–5 min after every injection of alfentanil, 5–7 min after every fentanyl injection and 13–15 min after every injection of morphine. One AEP averaged from 1000 responses with a stimulation rate of 9.3 represented approximately a 2-min period.

Statistical analysis. For the peak latencies V, Na, Pa, Nb and P1 and amplitudes Na/Pa, Pa/Nb and Nb/P1 (µV) were measured. For frequency analysis, a Fast-Fourier Transformation was used to calculate power spectra of the AEP. For each situation, AEP of each individual patient and an interindividual grand average calculated from the individual AEP of all patients in each group were analysed. Auditory evoked potentials were recorded awake and 3–5 min after every injection of alfentanil, 5–7 min after every fentanyl injection and 13–15 min after every injection of morphine. One AEP averaged from 1000 responses with a stimulation rate of 9.3 represented approximately a 2-min period.

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RESULTS

Figure 1 shows an original tracing of an auditory evoked potential (left side) and its power spectrum (right side) of an awake patient. V belongs to the brainstem-generated potentials (BAEP), which demonstrates that auditory stimuli were correctly transduced [1]. Na, Pa, Nb, P1 (MLAEP) are generated in the primary auditory cortex of the temporal lobe [1–6]; they are the electrophysiological correlate of the primary cortical processing of the
Fig. 2. Original tracings of AEP of three patients (one from the alfentanil, fentanyl and morphine groups). In the awake patients, BAEP can be identified easily. MLAEP show large amplitudes and a periodic waveform. During general anaesthesia with alfentanil, fentanyl and morphine, BAEP did not change. A significant increase in latency and reduction in amplitude of the late potential P1 were observed after the first injection of opioid. In contrast, the early cortical potentials Na, Pa and Nb showed only slight increases in latency and decreases in amplitude during general anaesthesia with alfentanil, fentanyl and morphine, corresponding with high energy of the AEP in the 30-40 Hz range in the power spectra. There was no dose-dependent effect of the agents on MLAEP and no difference between them with regard to their effects on MLAEP.

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Original tracings of AEP from three patients (one from the alfentanil, fentanyl and morphine groups) are shown in figure 2. The upper traces show the AEP of the awake patients. BAEP can be identified easily; MLAEP show large amplitudes and a periodic waveform. AEP of the awake patients have their maximal energy within the 30–40 Hz frequency range. During general anaesthesia with alfentanil, fentanyl and morphine, BAEP did not change. They are identical with those recorded in the awake state. With increasing doses of alfentanil, fentanyl and morphine, significant latency increase and amplitude reduction of the late potential P1 may be observed. This effect occurred after the first opioid injection. Additional doses of opioids caused no further reduction of P1 amplitude. In contrast, the early cortical potentials Na, Pa and Nb showed only slight...
increases in latencies and decreases in amplitudes during general anaesthesia with alfentanil, fentanyl and morphine. They showed a pattern similar to those recorded in the awake state, corresponding with AEP high energy in the 30-Hz range of the power spectra. There was no dose-dependent effect of alfentanil, fentanyl and morphine on MLAEP and no difference between alfentanil, fentanyl and morphine in their effects on MLAEP.

The same pattern was seen in the interindividual grand averages of the individual AEP with alfentanil, fentanyl and morphine (fig. 3). The high average rate, an increased signal-to-noise ratio and interindividual differences, especially in the late latency range (P1), led to a slight flattening of the potential. Again, AEP of awake patients showed large peak-to-peak amplitudes and a periodic wave form. After the first injection of opioid, P1 showed a significant increase in latency and decrease in amplitude. In contrast, BAEP and the early cortical potentials Na, Pa and Nb changed only slightly compared with the awake state.
During general anaesthesia with alfentanil, fentanyl and morphine, they could be recorded and identified. Mean (SD) values of the latencies of V, Na, Pa, Nb and P1 and showed a greater interindividual variability than latencies. The influence of the volatile anaesthetics isoflurane, enflurane and halothane on MLAEP has been investigated [7, 8, 14, 15]. With volatile anaesthetics, brainstem components of the auditory evoked potential are prolonged only slightly in latency. In contrast, mid-latency components show typically a dose-dependent increase in latencies and a decrease in amplitudes. At about 1 MAC isoflurane, MLAEP components are suppressed almost completely [7]. Initial transduction of auditory stimuli remains intact and auditory stimuli can be processed up to a brainstem or mid-brain level. In contrast, processing of auditory stimuli is blocked at the level of the primary auditory cortex.

Results obtained from sensory evoked potentials recorded in other modalities under volatile anaesthetics are in accordance with these findings. The early and late cortical components of visual and somatosensory evoked potentials are suppressed during anaesthesia with isoflurane, enflurane and halothane [16-23]. These studies demonstrate that volatile anaesthetic agents induce a general suppression of the afferent stimulus conduction and processing within the different sensory channels in the central nervous system. One possible explanation for the general suppression of cortical components in evoked potentials might be that volatile anaesthetics affect many different excitable biological membranes in the human cortex. Interaction between volatile anaesthetics and the phospholipid bilayers of the neural membrane blocking stimulus processing has been proposed [24].

<table>
<thead>
<tr>
<th>GROUP</th>
<th>V (ms)</th>
<th>Pa (ms)</th>
<th>Nb (ms)</th>
<th>P1 (ms)</th>
<th>Na/Pa (µV)</th>
<th>Pa/Nb (µV)</th>
<th>Nb/P1 (µV)</th>
</tr>
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<tbody>
<tr>
<td>ALF</td>
<td>1</td>
<td>6.43 (0.45)</td>
<td>32.23 (2.28)</td>
<td>47.08 (3.22)</td>
<td>1.16 (0.43)</td>
<td>1.22 (0.58)</td>
<td>1.15 (0.65)</td>
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<td></td>
<td>2</td>
<td>6.48 (0.65)</td>
<td>34.69 (2.31)</td>
<td>54.78 (6.78)</td>
<td>0.95 (0.49)</td>
<td>0.96 (0.59)</td>
<td>0.50 (0.42)</td>
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<tr>
<td></td>
<td>3</td>
<td>6.46 (0.46)</td>
<td>38.09 (4.71)</td>
<td>59.60 (9.47)</td>
<td>0.70 (0.39)</td>
<td>0.76 (0.37)</td>
<td>0.29 (0.26)</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>6.53 (0.61)</td>
<td>38.10 (4.75)</td>
<td>60.56 (9.14)</td>
<td>0.76 (0.37)</td>
<td>0.63 (0.30)</td>
<td>0.24 (0.25)</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>6.34 (0.27)</td>
<td>35.84 (2.18)</td>
<td>54.32 (8.24)</td>
<td>0.74 (0.23)</td>
<td>0.91 (0.55)</td>
<td>0.44 (0.40)</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>6.42 (0.30)</td>
<td>37.48 (2.89)</td>
<td>58.10 (4.75)</td>
<td>0.96 (0.59)</td>
<td>0.63 (0.30)</td>
<td>0.35 (0.28)</td>
</tr>
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</table>

During general anaesthesia with alfentanil, fentanyl and morphine, a marked and statistically significant increase in latencies of Nb and P1 occurred. This effect was seen after the first or second injection of alfentanil, fentanyl or morphine and remained stable with increasing administration of opioid. In contrast, BAEP did not increase and the early cortical potentials Na and Pa increased only slightly with increasing doses of alfentanil, fentanyl and morphine. Nevertheless, this reached statistical significance during general anaesthesia with alfentanil, and showed a greater interindividual variability than latencies. The influence of the volatile anaesthetics isoflurane, enflurane and halothane on MLAEP has been investigated [7, 8, 14, 15]. With volatile anaesthetics, brainstem components of the auditory evoked potential are prolonged only slightly in latency. In contrast, mid-latency components show typically a dose-dependent increase in latencies and a decrease in amplitudes. At about 1 MAC isoflurane, MLAEP components are suppressed almost completely [7]. Initial transduction of auditory stimuli remains intact and auditory stimuli can be processed up to a brainstem or mid-brain level. In contrast, processing of auditory stimuli is blocked at the level of the primary auditory cortex.

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The effects of opioids on MLAEP differ: there was no or only a slight increase in the latencies of Na and Pa and a slight decrease in their amplitudes. Only Nb and P1 latencies increased and P1 amplitude decreased significantly after the first or second injection of opioid. In contrast, BAEP and the early cortical peaks Na and Pa remained stable or changed only slightly, even after the largest opioid doses (alfentanil 500 \( \mu g \) kg\(^{-1} \), fentanyl 50 \( \mu g \) kg\(^{-1} \), morphine \( 3 \) mg kg\(^{-1} \)). They are similar to those in the awake state. There were no dose dependent effects of opioids on MLAEP and no differences between alfentanil, fentanyl and morphine with regard to their effects. Because Na, Pa and Nb are generated in the primary auditory cortex of the temporal lobe [1-6], auditory stimuli may be processed, at least partly, in the primary auditory cortex in the presence of high-dose opioids.

It is important to note that only the late latency of P1 increased and its amplitude decreased significantly with the opioids. This effect was the same for alfentanil, fentanyl and morphine. This phenomenon was observed after induction of general anaesthesia with the first bolus injection of opioid and the patient's loss of consciousness. Animal studies, and studies in humans, provide evidence for a functional interdependence between the wake-sleep rhythm, the activity of the ascending reticular activating system and the P1 amplitude [25, 26]. Most probably, P1 is generated by mesencephalic structures, the cholinergic cells of the pedunculopontine tegmental nucleus [27, 28]. They provide input to ascending projection pathways to thalamic nuclei. These are part of the ascending reticular activating system and are involved directly in wake-sleep behaviour. A significant reduction in P1 amplitude can be observed during natural sleep, especially during slow-wave sleep. It is reversible during rapid eye movement sleep episodes. Furthermore, the P1 amplitude can be correlated with the different sleep stages defined by EEG brain activity [25, 26]. Therefore, P1 amplitude changes were interpreted as an electrophysiological correlate of changes in vigilance and changes of the tonic activity of the ascending reticular activating system.

Neurophysiological investigations provide evidence that the ability to perceive and process auditory stimuli is preserved even in states of reduced vigilance. Furthermore, many studies indicate that, during states of reduced awareness, auditory information can be stored in the memory and recalled afterwards by non-conscious implicit memory function without any knowledge of the circumstances under which the individual gained that information [29, 30]. The likelihood of information being processed and recalled depends on the personal and emotional relevance of the auditory message.

The pattern of MLAEP changes with high-dose opioids seemed to be similar to that recorded during natural sleep. With opioids, there was only a slight slowing of cortical stimulus transmission and cortical stimulus processing in the auditory modality. In contrast with volatile anaesthetics (halothane, enflurane, isoflurane), opioids cannot suppress auditory stimulus processing in the primary auditory cortex completely and in a dose dependent fashion—processing of auditory stimuli in the primary auditory cortex remains intact to some extent.

Kileny, Dobson and Gelfand [31] investigated the effect of hypothermia on auditory evoked potentials during cardiac surgery. They showed that increasing hypothermia and reduced perfusion pressure induced prolongation of peak latencies of MLAEP, whereas high-dose opioid analgesia did not change MLAEP or brainstem-generated potentials [31, 32]. In accordance with these results, early cortical components of somatosensory and visual evoked potentials remain stable under opioids [18, 19, 21, 33, 34]. Furthermore, an auditory evoked steady state response (ASSR), which can be recorded in the processed EEG, seems to be correlated with adequate sensory information processing and the state of consciousness. The ASSR is suppressed under 1 MAC of volatile anaesthetics. In contrast, under opioids the ASSR is affected only slightly [35, 36]. This is a further indication that opioids may suppress sensory information processing and consciousness less reliably than volatile anaesthetics.

Opioid receptors are located in the dorsal horn of the spinal cord, the periaqueductal grey, the raphe nuclei, the medulla oblongata, the thalamus and the limbic system. They have analgesic, sedative, antitussive and ventilatory depressant effects. The \( \mu \) receptor mediates analgesia, change of emotional state and vigilance in the sense of euphoria and sedation by inhibiting the afferent input to the limbic system [37]. General suppression of the classical non-nociceptive sensory pathways, as achieved with volatile anaesthetics, cannot be documented with opioids. This corresponds well with clinical reports of intraoperative awareness and perception of auditory stimuli if opioids only are used during general anaesthesia [38-46]. Opioids, even in very large doses, do not always provide a reliable suppression of auditory stimulus processing during anaesthesia. Our data indicate that volatile agents (enflurane or isoflurane) provide a more reliable suppression of auditory stimulus perception and processing, and probably intraoperative awareness, compared with high-dose opioids.

REFERENCES

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