Changes in cortical electrical activity during induction of anaesthesia with thiopental/fentanyl and tracheal intubation: a quantitative electroencephalographic analysis

I. Rundshagen1*, T. Schröder1, L. S. Prichep2, E. R. John2 and W. J. Kox1

1Department of Anaesthesiology, University Hospital Charité, Humboldt University of Berlin, Campus Charité Mitte, Berlin, Germany. 2Brain Research Laboratories, NYU School of Medicine, New York, USA

*Corresponding author. E-mail: ingrid.rundshagen@charite.de

Background. There are regional differences in the effects of anaesthetics agents and peri-operative stimuli on the EEG. We studied the topography of the EEG during induction of anaesthesia and intubation in patients receiving thiopental and fentanyl to document regional electrical brain activity.

Methods. EEG was recorded in 25 patients in the awake state, after pre-medication, during induction, at loss of consciousness and after intubation. Eight bipolar recordings were made and the relative power of the frequency bands delta, theta, alpha, and beta were used (after z-score transformation for age) to measure changes in regional EEG activity.

Results. Noxious stimulation during tracheal intubation partially reversed the slowing of the EEG caused by anaesthesia. During induction of anaesthesia alpha activity was most reduced in temporal and occipital regions. The most prominent EEG changes after intubation were an increase in alpha and a decrease in delta power (P<0.001). The largest changes were in the frontal and temporal leads for alpha and in the frontal and central leads for delta. Heart rate and arterial pressure remained constant during intubation.

Conclusions. Changes in alpha and delta power were identified as the most sensitive EEG measures of regional changes in electrical brain activity during anaesthesia and noxious stimulation.

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Judgement of adequate anaesthesia remains a challenge.1 In clinical practice the anaesthesiologist often uses measurements of heart rate, arterial pressure, and observation of lacrimation, sweating and movement in combination with knowledge of anaesthetic pharmacology to judge the level of anaesthesia. The EEG has frequently been proposed to measure anaesthetic depth.2 Commercially available monitors, which are becoming more widespread, are practical and provide a single value from the complex spontaneous EEG, but whether these monitors can measure adequate depth of anaesthesia remains unclear.3,4 They are not a reliable measure for assessing nociception during anaesthesia.5 However, in many circumstances the EEG taken as a whole is well validated for identifying arousal by sensory stimulation.6,7

Topographical brain EEG mapping techniques, using multi-channel EEG recordings, can show distinct effects of anaesthetics on regional electrical brain activity.8–11 Quantitative EEG techniques can identify EEG features, which are sensitive to alterations in the state of consciousness, but are independent of the anaesthetic agent used.12 Surgical stimulation during standardized isoflurane–nitrous oxide anaesthesia increases delta and decreases alpha activities, which may be a ‘paradoxical’ arousal phenomenon, where lower EEG frequencies increase during noxious stimulation.13

EEG studies can indicate the cerebral pharmacodynamics of thiopental in humans.9,14–17 Delta activity is lost and higher EEG frequencies increase in frontotemporal brain regions during intubation under anaesthesia with thiopental/
nitrous oxide. We set out to measure multi-channel EEG during induction of thiopental/fentanyl anaesthesia and intubation to quantify regional changes in electroencephalographic power. The aim was to document EEG effects during clinical practice, when the doses of the anaesthetics were determined by the anaesthesiologist, to find out if the EEG would indicate arousal when the trachea was intubated.

Methods

Patients

After approval from the Institutional Ethics Committee and with written informed consent we enrolled 25 female patients (38 (8) yr, 60 (7) kg, height 1.65 (0.05) m (mean (SD)), ASA physical status I–II) about to have elective surgery. The patients had no neurological or psychiatric diseases and were not taking any medication.

Midazolam (0.1 mg kg⁻¹ orally) was given 45 min before anaesthesia. Anaesthesia was induced with thiopental and fentanyl. Non-depolarizing neuromuscular blocking agents were used to facilitate tracheal intubation. Neither the induction dose nor the time for intubation was standardized. The anaesthesiologist managing the procedure was to adjust the dosage individually and to decide when to intubate the patient.

EEG

Recordings were made with a Spectrum 32 EEG acquisition and analysis system (Cadwell Laboratories, Kennewick, WA). Nineteen electrodes were fixed to the scalp with paste, using the international 10/20 electrode placement system. In addition, electrodes were placed diagonally above and below the orbit of the eye, for detection of eye movement artefacts. An ECG lead was placed on the thorax and a ground electrode on the cheek. Eight bipolar derivations were calculated (Table 1).

The amplifiers had a bandpass of 0.5–70 Hz, with a 50 Hz notch filter. All impedances were kept below 5 kΩ, and checked regularly during the procedure. The A/D converter sampled at 200 Hz per channel with 12-bit resolution. The data were reduced to 100 Hz before analysis, using Fant’s resampling algorithm which minimizes aliasing. All EEG data were edited visually by an experienced EEG technician, aided by an automatic EEG artefact detection algorithm. At each condition defined below, an artefact-free sample of 2 min (48 segments, each of 2.5 s) was selected for quantitative analysis. After artefact removal, the EEG was converted from the time to the frequency domain using Fast Fourier Transform.

Measurements

To allow description of the topographical EEG changes during the anaesthetic and following noxious stimulation, five time points were chosen for further analysis. Baseline recordings were performed the day before the operation in the awake state. The patients rested comfortably with closed eyes during the recording. On the day of the operation the EEG recording was performed continuously. The EEG segments of interest were: (i) about 45 min following pre-medication, when the patients had arrived in the operation room (PREMED); (ii) after the bolus injection of fentanyl and thiopental (INDUCTION); (iii) after loss of consciousness, when the patient was unresponsive to verbal command and the eyelid reflex had disappeared (LOC); (iv) following intubation (INTUBATION). During the measurement INDUCTION an EEG segment of 30 s only (12 segments) was used, because the time to loss of consciousness varied widely between patients.

Statistical analysis

For each bipolar derivation, the relative power in each of four frequency bands was calculated: delta (1.5–3.5 Hz), theta (3.5–7.5 Hz), alpha (7.5–12.5 Hz), and beta (12.5–25 Hz). Using Neurometric QEEG procedures each EEG feature was transformed to obtain a normal distribution and then expressed as a z-score relative to the mean and standard deviation of the EEG feature obtained from normal data appropriate for the patient age. We present the z-scores of the relative power in each frequency band.

The statistical analysis was done with SPSS version 10.0 (Statistical Package for Social Science; SPSS Inc. Headquarters, Chicago, IL, USA). To analyse topographical EEG effects data from all measurements were subjected to multivariate two-factor analysis, separately conducted for each frequency band (8 EEG derivations × 5 time points). Multivariate comparisons were separately performed including baseline and LOC values. Data at LOC and INTUBATION were compared to assess changes induced.

<table>
<thead>
<tr>
<th>Bipolar EEG derivations</th>
<th>Left hemisphere</th>
<th>Right hemisphere</th>
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<tbody>
<tr>
<td>Central leads</td>
<td>C3/Cz</td>
<td>C4/Cz</td>
</tr>
<tr>
<td>Temporal leads</td>
<td>T3/T5</td>
<td>T4/T6</td>
</tr>
<tr>
<td>Fronto-temporal leads</td>
<td>T3F7</td>
<td>T4F8</td>
</tr>
<tr>
<td>Parieto-occipital leads</td>
<td>P3O1</td>
<td>P4O2</td>
</tr>
</tbody>
</table>

Table 1 The bipolar EEG montage (according to the international 10/20 system).
by noxious stimulation. The cardiovascular changes were analysed with multivariate analysis of variance (MANOVA: Hotellings t-square; repeated measurement design). P-values less than or equal to 0.05 were considered significant.

**Results**

**EEG**

MANOVA revealed significant main effects and interactions for the relative power at all frequency bands at the different EEG derivations over time (P=0.001). Details of multivariate and the post-hoc comparisons of the EEG data are listed in Tables 2 and 3. Maps of the group averages for alpha and delta power in each state are shown in Figure 1A and B.

**Effects of anaesthesia**

Significant interactions were found between time and topography for all frequency bands: the effect was most pronounced for alpha activity in the temporal and occipital regions. During loss of consciousness delta activity increased in all electrode positions (P<0.001). Theta activity increased in the temporal and parieto-occipital regions (P<0.001), and alpha and beta activity decreased in all regions (P<0.001).

**Effects of intubation**

During intubation delta activity decreased significantly in comparison with LOC at all electrode positions (P<0.001). At the frontal and central electrode positions delta power was no longer different from the baseline levels. Theta decreased only in both central and parieto-occipital brain regions (C3Cz, C4Cz; P<0.001 vs LOC). Alpha increased in all electrode positions (P<0.001 vs LOC) and remained significantly different from baseline in the temporal and parieto-occipital leads (T3T5, T4T6, P3O1, P3O4; P<0.001). In comparison with baseline, beta activity returned at all electrode positions to baseline values except in the central electrode positions (P=0.001 vs LOC). Considering the effects of tracheal intubation, topographical changes in alpha and delta were large in comparison to the other frequencies. The greatest changes were in alpha in the frontal and temporal regions and in delta in frontal and central leads (Table 2).

**Cardiorespiratory values**

These are given in Table 4. Changes did not reach statistical significance between the different states.

Loss of consciousness occurred 50 (20) s after injection of thiopental. The patients received 5.7 (0.2) mg kg⁻¹ thiopental (mean (SD), minimum 4.2, maximum 8.5 mg kg⁻¹). The dose of fentanyl was 3.0 (1.3) µg kg⁻¹ (minimum 1.3, maximum 7.7 µg kg⁻¹).

**Discussion**

This study supports previous evidence that induction of anaesthesia with thiopental as a sole agent or in combination
with other drugs slows the EEG with reduced alpha and beta frequencies and an increase in delta power.\textsuperscript{9} Multi-channel analysis showed that loss of power in the alpha frequency band was the largest effect, mainly in temporal and parieto-occipital brain regions, when the patient became unconscious. We did not see a biphasic EEG response (an increase in EEG frequencies at low drug concentrations followed by a decrease), as described in some studies, in any brain region.\textsuperscript{14 17} This feature is possibly only seen when plasma drug concentration changes slowly, as in studies of pharmacokinetics and pharmacodynamics. We monitored the EEG during routine anaesthetic administration.

At tracheal intubation the EEG showed marked changes at all frequencies. The greatest increases were in alpha frequency in the frontal and temporal brain regions and a loss of relative delta power in the frontal and central areas. Thus, the anaesthetic induced slowing of the EEG was in part reversed. This increase in higher EEG frequencies is
presumably a sign of cortical arousal by noxious stimulation. Arousal reactions in the EEG were described by Berger in 1930. During anaesthesia arousal reactions have been observed frequently in raw EEG traces and taken as a sign of light anaesthesia. We have found that EEG activation during intubation occurs in practice, when the dose of thiopental and fentanyl is judged adequate by an experienced anaesthesiologist. The resultant anaesthesia was not sufficient to block nociceptive input during intubation. It remains uncertain if this finding is clinically important, this question was not a part of the study design. It is possible that after a single dose of thiopental and fentanyl the effective drug concentration in the brain was decreasing when intubation was done, but it seems unlikely that these small changes in brain concentration could have had a great effect in generating these changes of EEG pattern that we noted.

Hung and co-workers used an aperiodic waveform analysis of the EEG, recorded from a left central parietal bipolar lead (C3P3), to assess EEG depth of anaesthesia and relate movement to serum thiopental concentration. This work supported others, with laryngoscopy and intubation as the most noxious stimuli. They estimated that a serum concentration greater than 80 μg kg⁻¹ was necessary to block movement at intubation, when thiopental was given alone. This concentration is far too high to be achieved by conventional induction doses of thiopental (4–6 mg kg⁻¹). They concluded that the large dose of thiopental necessary to ablate movement response in their study was a result of inadequate analgesia. Unfortunately we did not measure plasma concentrations of thiopental in the present study, which limits comparison with the study of Hung and co-workers. However, we demonstrated that cortical arousal is not blocked during induction of anaesthesia with thiopental and fentanyl. Surprisingly, Hung and co-workers did not report EEG changes after intubation or in response to less noxious stimulations, even with lower plasma concentrations of thiopental. This could be because the EEG was affected by movement artefacts, which interfere with interpretation of the EEG signal. In the present study the patients were paralysed, and we could exclude contamination of the EEG signal by muscle artefact. However, we could not use movement as a clinical sign of the level of anaesthesia. Another explanation for the difference of the two studies may be that aperiodic waveform analysis of the EEG is not sensitive enough to document cerebral arousal following noxious stimulation.

Wilder-Smith, Hagon and Tassonyi studied EEG arousal after laryngoscopy and intubation after a standard dose of thiopental (6 mg kg⁻¹) supplemented with nitrous oxide 50%. They analysed the change of the relative EEG power from a bilateral fronto-temporal EEG montage. Profound changes occurred in the relative delta, alpha, and beta power with the strongest effect seen for beta (an increase in activity of 647%). In the present study beta power returned to the corresponding baseline level (except in central brain regions), but alpha frequency was the most sensitive indicator of cortical arousal. The level of anaesthesia at the time of intubation was probably not the same in their study as in ours, because in our investigation the anaesthetic dose was titrated individually. We found no change in arterial pressure, while heart rate remained unchanged in both studies. The increase in arterial pressure in the former study was measured about 2 min after intubation, while it remained unchanged during intubation. We could have missed this change, because we measured the arterial pressure immediately after intubation. It is perhaps more likely, that the opioid we gave affected the responses and caused the difference in EEG and cardiovascular findings. Intubation increases plasma catecholamine concentrations, when patients were anaesthetized with thiopental.

Regional EEG changes with noxious stimulation during thiopental anaesthesia have not been studied previously. In patients anaesthetized with ketamine (3 mg kg⁻¹) and midazolam (0.15 mg kg⁻¹), an increase in delta, theta, alpha 1, and beta 2 power occurs in the temporo-parietal EEG regions during intubation. During isoflurane anaesthesia Kochs and co-workers showed that skin incision increased delta activity and decreased alpha activity mainly in frontal regions. The delta shift was attenuated by deeper anaesthesia (isoflurane 0.6 vs 1.2% in nitrous oxide 66%). These findings were attributed to the phenomena of intraoperative ‘paradoxical’ arousal. Both types of arousal responses in the EEG, ‘paradoxical’ arousal, a shift towards lower EEG frequencies, and the ‘classical’ arousal phenomenon, a shift towards higher EEG frequencies, have been described in the literature. The difference between our results and those two topographical studies might be explained by: (i) a different level of anaesthesia at the time of noxious input; (ii) different cerebral effects of the anaesthetics; (iii) different EEG techniques; or (iv) different noxious stimuli.

In conclusion, we found that changes in alpha and delta power were the most sensitive measures of electrical brain activity during anaesthesia and noxious stimulation. We could make adequate multi-channel EEG data measurements during clinical practice. However, off-line analysis limits the use of multi-channel EEG to assess changes of anaesthetic depth in clinical practice, but topographical

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Means (SD) of systolic, diastolic and mean arterial pressure (MAP) (mm Hg), percutaneous oxygen saturation (%) and heart rate (beats min⁻¹) at injection of thiopental (induction), after loss of consciousness (LOC) and after tracheal intubation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Induction LOC Intubation</td>
</tr>
<tr>
<td>Systolic</td>
<td>114 (18) 114 (19) 118 (24)</td>
</tr>
<tr>
<td>Diastolic</td>
<td>71 (8) 72 (13) 76 (13)</td>
</tr>
<tr>
<td>MAP</td>
<td>86 (15) 85 (16) 91 (16)</td>
</tr>
<tr>
<td>Oxygen saturation (%)</td>
<td>97 (3) 97 (3) 99 (1)</td>
</tr>
<tr>
<td>Heart rate (beats min⁻¹)</td>
<td>86 (17) 86 (16) 91 (18)</td>
</tr>
</tbody>
</table>
References

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electroencephalography shows the action of anaesthetics and their modification during noxious stimulation.

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