Continuous monitoring of depth of sedation by EEG spectral analysis in patients requiring mechanical ventilation

E. M. SPENCER, J. L. GREEN AND S. M. WILLATTS

Summary

Twenty-three patients undergoing intensive therapy had continuous EEG recording in an attempt to assess depth of sedation using spectral analysis. Median power frequency (MPF) and spectral edge frequency (SEF) were calculated and correlated with the clinical sedation score and blood concentration of sedative drug. Fifteen patients received isoflurane and eight midazolam. There was no correlation between MPF or SEF and sedation score or blood concentration of drug. These results suggest that no simple measure of the EEG is likely to correlate with depth of sedation in critically ill patients. (Br. J. Anaesth. 1994; 73: 649-654)

Key words
Anaesthesia, depth, Monitoring, electroencephalography.

Sedation is necessary for most critically ill patients in the intensive therapy unit (ITU). An objective means of assessing the level of sedation in unconscious patients undergoing ventilation would be helpful to prevent the hazards of inadequate or excessive sedation. In sedated patients electrophysiological techniques such as the electroencephalogram (EEG) and evoked potentials are the best possible sources of objective information on brain function. The availability of powerful, fast computer technology has led to the development of numerous devices which have been used for monitoring the EEG in conscious, anaesthetized and comatose patients.

There has been considerable interest in the use of the EEG in patients during anaesthesia in an attempt to obtain an objective means of assessing depth of anaesthesia. Although each anaesthetic agent has specific effects on the cerebral cortex, an overall pattern of change in the EEG can be discerned [1, 2]. These changes are less clear at depressed levels of consciousness associated with sedation. Nevertheless, there is an increase in the amount of fast activity initially, with a gradual shift to lower frequencies with increasing concentrations of both i.v. and inhalation anaesthetic agents, including isoflurane and midazolam [3-6].

The power spectrum is a useful method of displaying the computerized analysis of the EEG and many variables have been derived from the power spectrum in order to simplify the description and interpretation of these complex data. The EEG variables most commonly used to assess depth of anaesthesia are median power frequency (MPF) and spectral edge frequency (SEF). Rampil and colleagues established a correlation between shift in SEF and depth of anaesthesia [7]. Schwinden, Schuttler and Stoeckel established a relationship between plasma concentration of etomidate and MPF [8]. They have also established that, for methohexitone [9], isoflurane [10] and propofol [11], MPF of less than 5 Hz are associated with unconsciousness as defined by non-responsiveness to verbal commands. Thus closed-loop feedback control of anaesthesia by quantitative EEG analysis has been achieved in healthy volunteers.

Most of these studies were performed during anaesthesia, not sedation. Little work has been done with the EEG to assess the depth of sedation in seriously ill patients. The aim of the present study was to monitor the EEG continuously in the ITU in an attempt to correlate the EEG with clinical assessment of the level of sedation.

Patients and methods

Twenty-three critically ill adult patients who were expected to require controlled ventilation and sedation for longer than 24 h were allocated to receive either isoflurane or midazolam. The study was approved by the hospital Ethics Committee and informed written consent was obtained from the next of kin. Patients were excluded if there was any evidence of intracranial pathology, severe renal impairment (serum creatinine concentration > 200 μmol litre⁻¹), contraindications to opioids or benzodiazepines, or gross obesity (> 150% of ideal body weight). If patients required neuromuscular blocking drugs to establish controlled ventilation and adequate oxygenation they were excluded or withdrawn from the study.

The severity of illness in individual patients was assessed daily using the Apache II score. In all patients the lungs were ventilated mechanically with a Servo 900B ventilator. The tidal volume delivered was 8–15 ml kg⁻¹ at a ventilatory frequency necessary to maintain arterial carbon dioxide tension at 4–5 kPa. The inspired oxygen concentration was adjusted to maintain arterial oxygen tension > 10 kPa, and positive end-expiratory pressure was...
added as necessary. Major efforts were made to maintain basic physiological variables constant during monitoring.

Midazolam was prepared as a 0.1% solution and given at a rate of 0.05–0.1 mg kg\(^{-1}\) h\(^{-1}\). Subsequently the infusion rate was adjusted according to clinical signs. The rate of infusion of midazolam was recorded hourly and any changes were noted. Isoflurane was added continuously to the inspired air–oxygen mixture using a Siemens isoflurane vaporizer 952 mounted distal to the oxygen–air blender on a Siemens–Elema 900B ventilator. Initially the vaporizer setting was adjusted to deliver an inspired isoflurane concentration of 0.2%. Thereafter the vaporizer setting was adjusted to maintain an end-tidal isoflurane concentration of 0.1–0.6%, according to clinical signs. The inspiratory and end-tidal concentrations of isoflurane were monitored using a Siemens Servo Gas Monitor 120 and recorded hourly. Any changes made in the concentration of isoflurane were noted.

The degree of sedation was assessed initially and hourly thereafter on a scale modified from Ramsay (table 1). Score 1 represented inadequate sedation, scores 2, 3 and 4 were acceptable and scores 5 and 6 indicated that patients were sedated too deeply. The dose of sedative was adjusted to maintain a cooperative patient, who was orientated and tranquil or asleep, but responded to a loud auditory stimulus, for as much time as possible. During the period of sedation, patients' requirements for analgesia were assessed either by talking to the patient or by autonomic signs (tachycardia and lacrimation), and i.v. incremental doses of morphine 0.05 mg kg\(^{-1}\) were given for pain as required. The dose and times of all increments of morphine were recorded as were the timings of any noxious stimulation such as chest physiotherapy or cannula insertion.

Blood for measurement of isoflurane and midazolam concentrations was obtained regularly during the period of sedation. Midazolam and 1-hydroxy-midazolam concentrations were analysed using high-pressure liquid chromatography [12]. Within-batch variation for midazolam was 10.1% and for 1-hydroxy-midazolam 8.1%. Blood concentrations of isoflurane were determined by one-stage extraction with n-heptane followed by gas-liquid chromatography using electron capture detection [13]. Within-batch variation was 13%.

Monitoring of the EEG was started when the anaesthesia for surgery. The EEG was monitored continuously throughout the period of sedation.

A computer-based system was designed to be used online for signal analysis and for visualizing and recording the EEG pattern. The power spectral analysis uses fast Fourier transformation to transform epochs of raw data into its constituent frequency components which can then be presented graphically to show the relative power over the frequency of interest. Special attention was paid to the design of the screen display to allow two channels of raw EEG data to be displayed, as well as both channels of the power spectrum, as pattern recognition may help the ITU physician in making decisions.

The EEG was monitored by simple bilateral surface silver–silver chloride dome electrodes in a bipolar configuration linked to a differential amplifier. Electrodes were secured with collodion at F3–P3 and F4–P4 positions (international 10–20 system), referenced to the central forehead. The skin was prepared using Omni-Prep (electrode impedance was less than 5000 Ω during the study). Signals were amplified by an opto-isolated EEG amplifier with a 50 Hz notch filter, time constant of 0.1 s and low-pass filter at 30 Hz and at constant gain. A 12-bit analogue-to-digital converter (Transmed Ltd, Bristol, UK) sampling at 128 Hz and transputer board (Inmos UK Ltd) were used in a desktop computer to provide simultaneous raw and analysed data capture, display and storage to disk. Each channel of raw and processed data showing 0–32 Hz was displayed as a 4-s epoch, refreshed each 1 s. The compressed spectral array was displayed on a Siemens PT88 inkjet printer every 20 s.

The raw EEG was later inspected visually to exclude electrical or movement artefacts and only recordings devoid of artefacts were included in the analysis.

**Table 1** Sedation scale

<table>
<thead>
<tr>
<th>Sedation Score</th>
<th>Behavioural response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Anxious and agitated</td>
</tr>
<tr>
<td>2</td>
<td>Co-operative, accepting ventilation</td>
</tr>
<tr>
<td>3</td>
<td>Asleep. Brisk response to loud voice</td>
</tr>
<tr>
<td>4</td>
<td>Asleep. Sluggish response to loud voice</td>
</tr>
<tr>
<td>5</td>
<td>No response to loud voice</td>
</tr>
<tr>
<td>6</td>
<td>No response to pain</td>
</tr>
</tbody>
</table>

For pain as required. The dose and times of all increments of morphine were recorded as were the timings of any noxious stimulation such as chest physiotherapy or cannula insertion.

Blood for measurement of isoflurane and midazolam clinical levels of sedation, MPF and SEF were assessed by Spearman rank correlation.

**Results**

Patient characteristics are shown in table 2.

Mean concentration of isoflurane used for sedation was 2.9 (1.8–6.9) mg h\(^{-1}\). Mean morphine requirement was 0.92 mg h\(^{-1}\) in the isoflurane group and 0.85 mg h\(^{-1}\) in the midazolam group.

There was no correlation between end-tidal isoflurane concentration or midazolam infusion rate and sedation score. There was considerable variability in blood isoflurane and midazolam concentrations between patients but no correlation between blood drug concentrations and sedation score.

Mean duration of EEG recording was 18.5 (95% confidence limits 12.3, 24.6) h in the isoflurane group and 22 (13.4, 30.8) h in the midazolam group. For most patients EEG information was obtained for a wide range of sedation scores.

MPF and SEF results obtained from each patient were plotted against sedation score and examined
EEG monitoring of sedation

Table 2  Individual patient characteristics. Iso = Isoflurane, Mid = midazolam, S = survived, D = died

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Age (yr)</th>
<th>Sex (M/F)</th>
<th>Apache II score</th>
<th>Group</th>
<th>Duration of sedation (h)</th>
<th>S/D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emergency aortic aneurysm</td>
<td>59</td>
<td>M</td>
<td>8</td>
<td>Iso</td>
<td>29</td>
<td>S</td>
</tr>
<tr>
<td>Renal cancer</td>
<td>70</td>
<td>F</td>
<td>10</td>
<td>Iso</td>
<td>36</td>
<td>S</td>
</tr>
<tr>
<td>Sepsis</td>
<td>72</td>
<td>M</td>
<td>13</td>
<td>Iso</td>
<td>54</td>
<td>D</td>
</tr>
<tr>
<td>Emergency aortic aneurysm</td>
<td>73</td>
<td>M</td>
<td>17</td>
<td>Iso</td>
<td>20</td>
<td>D</td>
</tr>
<tr>
<td>Sepsis</td>
<td>75</td>
<td>M</td>
<td>22</td>
<td>Iso</td>
<td>36</td>
<td>D</td>
</tr>
<tr>
<td>Acute resp. failure</td>
<td>67</td>
<td>M</td>
<td>20</td>
<td>Iso</td>
<td>127</td>
<td>S</td>
</tr>
<tr>
<td>Emergency aortic aneurysm</td>
<td>66</td>
<td>M</td>
<td>14</td>
<td>Iso</td>
<td>20</td>
<td>D</td>
</tr>
<tr>
<td>Acute resp. failure</td>
<td>58</td>
<td>F</td>
<td>13</td>
<td>Iso</td>
<td>30</td>
<td>S</td>
</tr>
<tr>
<td>Thoracic aortic aneurysm</td>
<td>49</td>
<td>M</td>
<td>18</td>
<td>Iso</td>
<td>42</td>
<td>S</td>
</tr>
<tr>
<td>Multiple trauma</td>
<td>17</td>
<td>M</td>
<td>13</td>
<td>Iso</td>
<td>46</td>
<td>D</td>
</tr>
<tr>
<td>Acute resp. failure</td>
<td>52</td>
<td>F</td>
<td>12</td>
<td>Iso</td>
<td>24</td>
<td>S</td>
</tr>
<tr>
<td>Cardiovascular failure</td>
<td>71</td>
<td>M</td>
<td>20</td>
<td>Iso</td>
<td>24</td>
<td>S</td>
</tr>
<tr>
<td>Cardiovascular failure</td>
<td>45</td>
<td>M</td>
<td>23</td>
<td>Iso</td>
<td>43</td>
<td>S</td>
</tr>
<tr>
<td>Multiple trauma</td>
<td>25</td>
<td>M</td>
<td>15</td>
<td>Iso</td>
<td>53</td>
<td>S</td>
</tr>
<tr>
<td>Emergency aortic aneurysm</td>
<td>69</td>
<td>M</td>
<td>9</td>
<td>Iso</td>
<td>46</td>
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<tr>
<td>Perforated duodenal ulcer</td>
<td>69</td>
<td>F</td>
<td>15</td>
<td>Mid</td>
<td>32</td>
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 visually. There was considerable variation in the EEG both within and between patients. There was no obvious relationship from the plotted data between MPF or SEF and the clinical level of sedation (figs 1, 2).

To correlate the calculated EEG data with sedation score, some averaging was necessary. As the sedation score was recorded hourly (on the hour), MPF and SEF for each channel for each patient were averaged over the 5 min before the hour in an attempt to obtain as accurate a value as possible to correlate with sedation score. Mean MPF and SEF were regressed with the sedation score, using the Spearman rank correlation. Observation of the power spectrum suggested a trend towards less EEG variability in MPF and SEF at deeper levels of sedation. In order to examine this, the SD of the averaged MPF and SEF was regressed also with the sedation score. Initially all the patients were grouped together, then the two treatment groups were analysed separately and then each patient was analysed individually. No correlation was found between MPF or SEF and sedation score. There was also no correlation between sedation score and the SD, indicating similar variability of the EEG at all levels of sedation.

Multivariate analysis combines variables of a signal and manipulates them statistically to provide a weighting to give maximum discrimination of data [14, 15]. The power spectrum was divided into the 10 percentile frequency bands from 0–32 Hz, making up nine variables. Three more were derived from mean frequency, a “zero crossing” count and a “turns” analysis. The latter two required a signal reversal of more than 1% amplitude. The 12 variables were combined and two discriminate axes were derived from the data such that each axis was a weighted combination of the variables that best separated the data sets. This method showed good discrimination of the alert, sedated and overdosed states in volunteers undergoing sedation with enflurane [16].

![Figure 1](https://academic.oup.com/bja/article-abstract/73/5/649/367692/0)

![Figure 2](https://academic.oup.com/bja/article-abstract/73/5/649/367692/0)
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Both midazolam and isoflurane provide satisfactory
sedation in patients receiving midazolam or iso-
flurane. It was disappointing that no pattern was
demonstrated even within an individual patient. The
use of multivariate analysis is complex and needs
further evaluation. We chose 12 EEG variables for
our analysis but it might be more appropriate to
include other factors, such as physiological variables,
to assist in the assessment of depth of sedation.

To create the axes, EEG data were obtained from
several patients from the same treatment group at
three conscious levels: awake and relaxed (group 1),
sedated to score 2 (group 2) and sedated to score 5
(group 5). There appeared to be considerable overlap
between the three states (fig. 3).
In order to determine if a specific concentration of
either isoflurane or midazolam produced a particular pattern in the EEG, MPF and SEF were plotted
against drug concentration. There was no correlation
between plasma concentrations of either isoflurane,
midazolam or 1-hydroxy-midazolam and MPF or
SEF.

Discussion

Both midazolam and isoflurane provide satisfactory
dedation in patients requiring mechanical ventilation
[17]. In order to avoid excess sedation and its
complications, it is important to assess the depth of
sedation frequently. However, it is very difficult to
assess sedation objectively and produce a neat
quantitative score.

The EEG may provide a monitor of depth of
anaesthesia but there are practical difficulties with
recording the EEG continuously in the ITU. The EEG is a recording from the scalp of microvolt
differences in electrical potentials generated by the
underlying cortical tissue. In the ITU there are
many sources of interference which result in con-
siderably higher voltages than those generated by the
brain. Most EEG systems have a bandpass filter
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0.5–30 Hz helps to reduce electrical noise and artefact. A notch filter turned to the frequency of the
mains supply and fitted to the amplifier minimizes
mains interference. The differential amplifier reduces the interference of electrical equipment only if both
electrodes make good contact, and an automatic
impedance meter and alarm built into the system is
essential for continuous EEG recording. Artefacts
associated with movement or electrical interference
must be excluded.

For the EEG to be a useful monitor of depth of
sedation in the ITU, it must be monitored con-
tinuously and analysed in real-time. One of the
limitations of the use of a simple desktop computer
is that constraints in collecting, processing and
archiving data arise because processes must be
sequenced. Our approach of using a separate trans-
puter board for parallel multi-tasking allowed sim-
ultaneous presentation of raw data and processed
information to the clinician, in addition to collection
and archiving of data under transputer management.

Before a closed-loop feedback control system using
the EEG can be used in patients requiring sedation
in the ITU, some variable of the EEG must be
shown to correlate with clinical signs of depth of
sedation. Although at levels of surgical anaesthesia
there appears to be a dose-related increase in power
in the lower frequency bands resulting in decreased
MPF, this cannot be extrapolated to the changes
seen during sedation. During sedation with propofol,
Forrest and co-workers demonstrated a dose-related
decrease in MPF [18]. However, it has been shown
that propofol, administered to volunteers in sedative
doses, caused a significant increase in high frequency
beta power, most notably in the frontal and central
areas of the cerebral cortex [19]. The changes in high
frequency EEG power are reflected by changes in
both MPF and SEF but the change in MPF was
proportionally much larger. Changes in high fre-
quency EEG activity have been reported with several
i.v. sedative agents and low doses of inhalation
agents [1, 6, 20–22].

There has been little work on the use of the EEG
in the ITU to assess depth of sedation. Veselis,
Carlon and Bedford studied the effect of midazolam
sedation in patients undergoing ventilation in the
ITU [23]. A discrete period of EEG was recorded at
a specific sedation score. Only 42 observations were
made in 17 patients. SEF decreased significantly as
sedation deepened and SEF was found to be the
most sensitive of the measures tested and MPF the
least. The segments of EEG were stored on a
computer for later analysis. More recently, the same
group have shown that, in patients in the ITU
sedated with midazolam, total power remained fairly
constant across sedation levels but there was a
significant shift of power from high to low frequencies
as sedation increased [24]. They found that SEF was
a more sensitive indicator of depth of sedation than
MPF. They analysed only 68 EEG samples, each of
4 min duration, from 31 patients.

In our study we were unable to show a consistent
relationship between MPF or SEF and the level of
sedation in patients receiving midazolam or isof-
lurane. It was disappointing that no pattern was
demonstrated even within an individual patient. The
use of multivariate analysis is complex and needs
further evaluation. We chose 12 EEG variables for
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The EEG may provide a monitor of depth of
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Our data support Shearer, O'Sullivan and Hunter who were unable to correlate specific EEG patterns with sedation score [25]. Their study, in common with ours, recorded the EEG continuously for long periods of time, whereas Veselis and co-workers recorded only a few discrete runs. Opioids cause a gradual slowing of EEG frequency with an increase in large amplitude slow waves at high doses [26, 27] but we considered it inappropriate to withhold analgesia from our patients. Shearer's patients received opioids also during the study period whereas none of Veselis's patients had.

It was interesting that Veselis and colleagues showed that even at the lightest level of sedation, where response to verbal command occurs, there was an absence of high frequency power characteristically seen in volunteers [24]. A large portion of EEG power at all sedation levels was in the delta region, indicating that satisfactory levels of sedation in critically ill patients correspond with significant CNS depression. This demonstrates that the results of work carried out in healthy subjects cannot be extrapolated to this group of patients.

The EEG may not be normal in seriously ill patients. Many factors affect the EEG, such as impaired cerebral oxygen delivery (as a result of hypoxia or hypotension) [28], alterations in carbon dioxide tension [29] or body temperature [30]. Generalized EEG abnormalities may occur with alterations in blood sugar, renal or hepatic failure, electrolyte imbalance, endocrine disorders and certain toxic-metabolic conditions [31, 32]. Patients in the ITU receive many drugs which may have an effect on the EEG also.

We were unable to find any correlation between serum concentrations of either midazolam or isoflurane and the clinical sedation score. This supports previous work that there is large interindividual variation in pharmacokinetic and pharmacodynamic responses in critically ill patients [33, 34].

There have been no previous attempts to record the EEG continuously in the ITU to assess the level of sedation. Our results showed that there was no correlation between MPF or SEF and the depth of sedation. The variability within the same patient suggests that no simple single measure of the EEG is likely to correlate with the level of sedation in this group of patients.

Recently there has been considerable interest in the use of evoked potentials to assess depth of anaesthesia. The auditory evoked response (AER), in particular the early cortical component, has been shown to change in response to increasing concentrations of both i.v. and volatile anaesthetic agents [35-37]. Characteristic changes also occur at low concentrations of anaesthetic, reflecting the change between wakefulness (responding to command) and light anaesthesia (no response) [38, 39]. In contrast, there were no dose-dependent effects of opioids on the early cortical AER [40].

The late cortical response of the AER reflects neural activity of the association cortex and is influenced by processes of stimulus evaluation and cognitive analysis. Event-related potentials, such as the late cortical waves are abolished by clinical concentrations of anaesthetic and sedative agents. Whereas these late cortical waves may be of interest to study the more sophisticated aspects of cerebral function and the detection of intraoperative awareness, it is unlikely that they will be useful as a measure of depth of sedation.

Acknowledgements

The EEG equipment was purchased with a grant obtained from the Bristol and Weston District Research Committee. We thank Dr Hilary Morgan and Mrs Phil Alden, Department of Neurophysiology, for their assistance and Mrs Shirley Gorman, Sir Humphry Davy Department of Anaesthesia, for performing the isoflurane and midazolam analyses.

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