QUANTITATIVE EEG ANALYSIS DURING ANAESTHESIA WITH ISOFLURANE IN NITROUS OXIDE AT 1.3 AND 1.5 MAC

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The rational and efficient use of EEG monitoring devices in the perioperative period requires a body of data which characterizes those EEG changes expected during anaesthesia. Although isoflurane has been studied intensively in the past decade, only a few studies (Brandt and Pokar, 1984; Clark et al., 1973; Dworacek and De Vlieger, 1984; Eger, Stevens and Cromwell, 1971; Poulton and Ellingon, 1984) considered the EEG changes associated with isoflurane anaesthesia. Moreover, much of the available information is qualitative, or semiquantitative, rather than of a quantitative nature.

The purpose of this study was to evaluate the EEG during clinical anaesthesia with isoflurane and nitrous oxide (in oxygen) at 1.3 and 1.5 MAC, and to study the distribution of various spectral EEG variables during surgery, and in the perioperative period.

PATIENTS AND METHODS
Fourteen patients without apparent neurological deficit participated in the study. They were randomly allocated to two groups (n = 7) anaesthetized with isoflurane plus 60% nitrous oxide (in oxygen) at 1.3 and 1.5 MAC, and to study the distribution of various spectral EEG variables during surgery, and in the perioperative period.

SUMMARY
In 14 patients undergoing elective surgery the EEG was studied during anaesthesia with isoflurane and nitrous oxide (in oxygen) at 1.3 and 1.5 MAC. The distributions of spectral EEG indices of the baseline EEG, during the intraoperative and recovery periods were established and compared. Median frequency exhibited the most clear separation between the distributions during recovery and the intraoperative period. During anaesthesia, the median values were found to be lower than 5 Hz; when the patient was conscious, the EEG median frequency values were greater than 6 Hz. Time to recovery was 13.4 ± 2.9 min and 30.0 ± 8.5 min for the groups treated with 1.3 and 1.5 MAC, respectively. Burst suppression was observed during the loading period in all patients treated with 1.5 MAC and in five patients out of seven receiving 1.3 MAC. The average duration of the period of burst suppression was markedly greater in the group receiving 1.5 MAC than in the group receiving 1.3 MAC. It is concluded that devices designed for EEG trend monitoring during anaesthesia should preferably depict a frequency measure, and allow for burst suppression recognition before spectral analysis.

Anaesthetic procedure
Anaesthesia was induced with thiopentone 5 mg/kg body weight. Pancuronium and suxamethonium were administered. Once the trachea had been intubated, anaesthesia was maintained with 60% nitrous oxide and isoflurane in oxygen. Isoflurane was administered according to a scheme based on pharmacokinetic considerations consisting of an initial loading period of 15 min, followed...
by a lower vaporizer setting for the following 105 min which again was decreased if isoflurane was administered for longer than 2 h. This regimen led to almost constant end-tidal (Normac (Datex)) concentrations after 25–30 min (Schwilden et al., 1985). The data of the pharmacokinetic model (Davis and Mapleson, 1981; Lowe and Ernst, 1981) were individualized by estimating cardiac output, lean body mass and fat tissue from body weight and body height (Fiserova-Bergrova, Vlach and Casady, 1980).

Table I presents for both groups the demographic data as well as the durations of the administration of isoflurane and the times between intubation and extubation. End-tidal $P_{CO_2}$ tension was measured breath-by-breath (Capnometer 47210A, Hewlett-Packard) and ventilation was adjusted to maintain the end-tidal $P_{CO_2}$ between 4.5 and 4.8 kPa. Fresh gas flow was at least 0.5 litre min$^{-1}$ greater than minute ventilation. Body temperature was kept greater than 36 °C.

Surgery was commenced not earlier than 15 min after the loading period, that is 30 min after the start of the isoflurane. At the end of surgery 100% oxygen was administered and neuromuscular blockade was antagonized with neostigmine. During the recovery period patients were frequently asked to respond to verbal commands.

**EEG analysis**

The information from four EEG leads ($C_z$–$F_i$, $C_z$–$O_i$, $i = 1, 2$) was recorded on magnetic tape (PR 2200, Ampex). One of the two symmetrical leads $C_z$–$O_i$ ($i = 1$ or 2) was used for off-line signal analysis. The primary filter settings of the EEG amplifier (Mingograph Junior, Siemens) were 0.3 s and 70 Hz. For automatic analysis, the raw signal was filtered between 0.5 and 32 Hz and broken down into epochs of 8.192 s duration which were digitized at a rate of 125 Hz and 12 bit A–D resolution. For each epoch a set of eight EEG variables was calculated from the power spectrum between 0.5 and 32 Hz. Since the area under the power spectrum curve is proportional to the square of the mean amplitude (Bendat and Piersol, 1971), one may normalize the area under the power spectrum to one (normalized power spectrum) by extracting mean amplitude. Thus the entire dependence on absolute power of all EEG variables derived from the power spectrum can be focused on one quantity. From the normalized power spectrum the percentage of power in the frequency bands 0.5–2, 2–5, 5–8, 8–13 and 13–32 Hz was calculated as well as the median frequency—defined as the median (50% quantile) of the power spectrum regarded as a distribution (Schwilden and Stoeckel, 1980) and the 95% quantile (Hudson et al., 1983). Burst suppression was detected by an algorithm based on the local variance of the EEG signal before Fourier transformation and data smoothing. The duration of the period of suppression was expressed as a percentage of the duration of the total epoch. Artefact rejection was performed by visual inspection. For data smoothing a moving average over nine epochs was used.
RESULTS

The actual vaporizer settings (mean ± SD) were 1.74 ± 0.16 vol% and 2.20 ± 0.11 vol% for the induction period for the 1.3 and 1.5 MAC groups, respectively. These loading concentrations were followed by maintenance concentrations of 1.24 ± 0.08 vol% and 1.57 ± 0.05 vol%, respectively.

During the loading period burst suppression patterns were seen in all patients in the group receiving 1.5 MAC, and in five patients in the group receiving 1.3 MAC. On average the duration of the period of suppression was shorter for patients receiving 1.3 MAC. Expressing the period of suppression as a percentage of the epoch duration (8.192 s), figure 1 compares the development of burst suppression (group average) with the commencement of isoflurane administration. Although the highest alveolar concentrations were

![Graphs showing EEG activity over time for 1.3 and 1.5 MAC concentrations.](https://example.com/figure1)

Fig. 2. Comparison of the time course of percentage of total EEG activity in the frequency bands indicated for two individuals of each group. ↑ = Induction of anaesthesia with thiopentone; — = administration of isoflurane and nitrous oxide.
reached after terminating the loading period, the average duration of suppression did remain stable for a time.

Figure 2 gives two typical examples of the time course of activity, in the frequency bands indicated, for the group receiving 1.3 MAC (left hand side) and the group receiving 1.5 MAC. Both examples demonstrate that the theta band (5–8 Hz) changes little. It was only affected during induction and recovery, when activity moved from the high frequency bands (alpha and beta band) to the low frequency bands (< 5 Hz). The band 0.5–2 Hz can acquire up to 60% of total power. The median frequency, 95% quantile and mean amplitude, which are independent of the frequency band structure are depicted in figure 3. Both frequency measures, median and 95% quantile, exhibited consistently a decrease with increasing depth of anaesthesia; only at low concentrations—during induction and recovery—was activation of the high frequency bands, leading to transient increases in both measures of frequency, observed. Median frequency and 95% quantile were consistently lower in the patients receiving 1.5 MAC compared with 1.3 MAC.

### Table II. Distributions of various EEG variables during surgery (percentage of activity in the frequency bands 0.5–2 Hz, 2–5 Hz, 5–8 Hz, 8–13 Hz, 13–32 Hz; median frequency (Hz); 95% quantile of EEG power spectrum (Hz) and mean amplitude (μV)) at the 5%, 25%, 50%, 75% and 95% quantiles. †Calculated according to formula (1); serves as a measure of the difference between two corresponding distributions

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TABLE III. Distributions of various indices of EEG activity during surgery (percentage of activity in the frequency bands 0.5-2 Hz, 2-5 Hz, 5-8 Hz, 8-13 Hz, 13-32 Hz; median frequency (Hz), the 95% quantile of EEG power spectrum (Hz) and mean amplitude (μV)) for the five selected quantiles for both groups. It is difficult to decide by statistical means whether two corresponding distributions are different or not. This is because one does not know to what extent two EEG epochs from which the variables are calculated can be regarded as independent events, thus affecting directly the degree of freedom of the distributions. Hence the t value cannot be used to test the hypothesis, but can be used to compare distances between distributions. From a clinical point of view, the large overlap between the distributions makes it virtually impossible to predict for a given EEG epoch, on the basis of the investigated variable, whether it belongs to the group treated with 1.3 or 1.5 MAC. Adopting this standpoint in table III, the distributions for 1.3 and 1.5 MAC are combined and compared with the distribution for the baseline EEG and the EEG recorded during the recovery period after having responded to command (“open your eyes”) until cessation of EEG recording.

A graphical representation of the distribution of the variables is given in figure 4. It compares the baseline EEG (left hand side) with the intraoperative EEG (dashed) and the EEG during the recovery period. The most pronounced overlapping of the distribution during the recovery and intraoperative period is associated with the theta band (5-8 Hz), while the median frequency is the best discriminator between both periods. The mean time from cessation of isoflurane and nitrous oxide administration to response to commands was 13.4±2.9 min for the group with 1.3 MAC and 30.0±8.5 min for the group with 1.5 MAC. Trying to relate this time to the average values of the EEG variables 5 min before the end of surgery resulted in a non-significant relationship for each variable.

**DISCUSSION**

This study attempted to establish a quantitative basis for the EEG during anaesthesia with isoflurane at 1.3 and 1.5 MAC in 60% nitrous oxide and oxygen. The choice of these two concentrations was based on observations that, in most patients, clinical anaesthesia is achieved at alveolar concentration of 1.3 MAC or greater (Lowe and Ernst, 1981). The clinical impression that the quality of anaesthesia in both groups did...
not differ to any apparent degree, might be reflected by the rather similar EEG behaviour observed in both groups during the surgical procedure. This might be an indication that the two isoflurane concentrations studied lie within the upper range of the isoflurane concentration–spectral EEG effect relationship. On the other hand one could argue that both concentrations lie too close to each other to cause significant differences. The vaporizer settings of isoflurane for 1.3 MAC and 1.5 MAC with 60% nitrous oxide differ, however, by more than 25%. This

Fig. 4. Distribution of the investigated indices of EEG activity during various clinical periods. The distributions of both group (1.3 MAC and 1.5 MAC) have been merged. The first five indices depict the distribution of the percentage of total EEG activity in the indicated frequency band. The left hand side depicts the distributions for the baseline EEG, the right hand side shows the corresponding distributions during surgery (shaded) and during recovery after having responded to command.
percentage increase in concentration leads to a marked prolongation in recovery at the end of surgery, and to quite different durations of burst suppression during the loading phase. As shown in this study, and as reported by others, burst suppression patterns can occur within the range of concentrations used in clinical practice (Eger, Stevens and Cromwell, 1971; Newberg, Milde and Michenfelder, 1983) and have immediate implications for the use of EEG monitoring devices based on spectral indices. Since burst suppression violates the assumptions (Schwilden and Stoeckel, 1985) underlying power spectrum analysis, and may cause misleading interpretations (Schwilden and Stoeckel, 1980; Levy, 1984), it is advisable to detect evidence of burst suppression before undertaking power spectrum analysis. The recognition of these patterns before spectral analysis may give relevant clinical information. In our experience, the presence of burst suppression indicates a depth of anaesthesia which is greater than that necessary to ensure unconsciousness and to prevent recall and awareness. On the other hand, it indicates that cerebral metabolism is decreased (Newberg, Milde and Michenfelder, 1983)—a feature which may, under certain circumstances, be regarded as a desirable therapeutic aim associated with anaesthesia.

Among the spectral variables studied, the median frequency showed the greatest degree of discrimination between the intraoperative period and the recovery phase. The spread of its distribution during the intraoperative period had an upper limit of about 5 Hz, and comparison of this distribution with that obtained once the patient had responded to command led to the conclusion that awareness recurs at the transition from median values less than 5 Hz to median values greater than 5 Hz. This is in agreement with earlier observations made with other drugs (Schwilden and Stoeckel, 1980; Schwilden, Schütter and Stoeckel, 1985). Other authors have recommended the so-called “edge frequency” (Rampil et al., 1980) as a correlate of the depth of anaesthesia. However, as yet, its precise definition has not been published. Hudson and colleagues (1983), therefore, used the 95% quantile of the power spectrum distribution instead of the edge frequency. The problems with this index are that it is highly dependent on minor activities in the high frequency bands and reflects poorly the centre of the power spectrum distribution and the activities in the low frequency bands.

Some EEG monitoring devices neglect or attenuate the activities in the low frequency range (0.5–2 Hz) because most movement artefacts induce artificial low frequency activity. In the light of the finding that this band may contain up to 60% of total activity during anaesthesia, it could be disadvantageous to omit this band.

Although it is evident that a complex and, in general, multimodal distribution like an EEG power spectrum cannot be described fully by one index (Levy, 1984), it seems to be reasonable, on the basis of the results presented, to characterize the gross shifts of EEG frequency associated with anaesthesia by the median of the power spectrum.

We conclude that EEG devices designed to monitor trends of spectral correlates of depth of anaesthesia should allow low filter settings down to 0.5 Hz, depict some frequency measure, preferably the median EEG frequency, and be able to detect burst suppression, which may be characterized by the duration of the period of suppression either in absolute time or in time relative to the duration of the processed EEG epoch. The advantage of such a device in clinical practice is indicated by the results of this study. In order to minimize time to recovery, one would choose isoflurane concentrations as low as possible. Too low concentrations, however, risk too light a plane of anaesthesia. Median frequency values greater than 6 Hz can indicate awareness, as shown in figure 4 and table III. Especially when using neuromuscular blocking agents, this might be the only indication of awareness. Thus, titrating isoflurane concentrations so that median frequency values remain below those values associated with awareness, could help prevent too light planes of anaesthesia. The recognition of burst suppression, on the other hand, may help either to avoid too deep levels of anaesthesia or to confirm that brain metabolism is decreased.

REFERENCES


