The electroencephalographic Effects of Desflurane in Humans


The electroencephalographic (EEG) effects of a new inhaled anesthetic are of interest because of the potential of such agents to produce excitatory (convulsant) activity and because of the potential usefulness of the EEG as an indicator of anesthetic depth and cerebral activity. Accordingly, we examined the EEG in 12 healthy, young male volunteers during desflurane anesthesia. Each subject had a baseline recording and then steady-state exposure to 6, 9, and 12% (0.83, 1.24, and 1.66 MAC) desflurane in O₂ alone, and to 3, 6, and 9% desflurane in O₂ with 60% N₂O. The sequence of doses and the presence of N₂O were randomized. We used mechanical ventilation to maintain normocapnia at each dose level. We also tested the effects of hypercapnia secondary to spontaneous ventilation. Additionally, at 1.24 MAC, subjects’ lungs were hyperventilated to a Paco₂ of 25.8 ± 0.7 mmHg and exposed to rhythmic, loud clapping to attempt to provoke excitatory phenomena. Finally, after at least 6 h exposure to desflurane, we repeated measurements at 0.83 and 1.66 MAC to assess possible tolerance. Four channels of EEGs were monitored visually, and at each dose, a quantitative EEG analysis was performed. Desflurane produced EEG changes comparable to those observed with equipotent levels of isoflurane. No epileptiform activity was seen. Desflurane significantly suppressed EEG activity; prominent burst suppression was seen at 1.24 MAC and higher. Substitution of N₂O for 0.42 MAC desflurane reduced the degree of EEG suppression relative to the equipotent administration of desflurane and O₂. Quantitative EEG measures for the early doses and for the later, repeated exposures did not differ. (Key words: Anesthetics, gases: nitrous oxide. Anesthetics, volatile: desflurane (I-653). Brain: electroencephalogram.)

DESFLURANE, a derivative of isoflurane, has lower solubility than isoflurane and therefore more rapid pharmacokinetics.¹ Halogenated ethers, a class of potent anesthetics to which these drugs belong, have a wide range of effects on electroencephalographic (EEG) activity and brain metabolism. Isoflurane, for example, causes profound EEG depression,² whereas enfurane at higher concentrations may cause epileptiform activity, particularly in the presence of hypoxia.³ Flurothyl (Indoklon) is a potent epileptogen.⁴ Clinical evaluation of desflurane, as a halogenated ether, should determine whether it causes a depression of brain electrical activity or, conversely, a potentially detrimental excitement.

Previous studies in juvenile swine indicate that desflurane produces dose-related depression of EEG activity, up to and including burst suppression. In this animal, increasing doses of desflurane produced EEG depression statistically indistinguishable from that produced by isoflurane in approximately equipotent concentrations.⁵ The current report extends these studies to humans. We report the EEG response of normal, young volunteers to graded concentrations of desflurane with or without N₂O, at high, low, and normal levels of arterial CO₂ tension (Paco₂). The study protocol was approved by the Human Experimentation Committee of the University of California, San Francisco. We enrolled 12 healthy, young male volunteers aged 23.8 ± 2.6 yr (mean ± SD) after obtaining informed, written consent. Selection criteria used to determine eligibility included: absence of neuropsychiatric disease and complete abstinence from recreational drug use, including alcohol. Subjects fasted for at least 8 h and refrained from any drugs that might have central nervous system effects, including caffeine and tobacco, for at least 12 h before the study. No preanesthetic medication was given.

On the morning of study, subjects reclined supine, and pressure points were carefully padded. A left radial arterial catheter was inserted to monitor arterial pressure and to obtain samples for blood gas analysis. Eight 30-G, subdermal needle electrodes (model E-2, Grass Instruments, Quincy, MA) were placed in the following International 10–20 System locations: FP1, FP2, C3, C4, P3, P4, O1, and O2 to create a bilateral, bipolar frontocentral, and parietooccipital montage. The electrodes were adjusted, if necessary, to balance all contact impedances between 5–10 kΩ. The needle electrodes were well tolerated by all subjects. After electrode placement, subjects rested with room lights dimmed and eyes closed for at least 20 min before we recorded a baseline EEG.

The anesthetic study design was a semirandomized exposure to desflurane 6, 9, and 12% (0.83, 1.24, 1.66 MAC respectively) and, in some subjects, 15% (2.08 MAC). The two lowest concentrations were administered first, in random order, followed by 1.66 MAC. We choose this sequence because the hemodynamic effects of moderate-
to-high doses of desflurane were not known at the outset of the study, and there was concern that the 1.66 MAC dose induced excessive hypotension. Subjects who tolerated 1.66 MAC well also received 2.08 MAC.

N₂O was administered to all subjects in a crossover design in which 60% N₂O was substituted for 3% (0.42 MAC) desflurane. The concentration sequence was repeated for both desflurane in O₂ and desflurane and N₂O in O₂. The use of N₂O for induction and first sequence was randomized and resulted in six subjects’ receiving the N₂O combination first.

Anesthesia was induced by inhalation of desflurane with or without N₂O via mask. The trachea was intubated without the use of adjuvant drugs. Mechanical ventilation was adjusted to produce a PaCO₂ of 30–35 mmHg, and normothermia was maintained with a Bair Hugger® forced-air warmer (model 200, Augustine Medical, Eden Prairie, MN).

Anesthesia was induced with desflurane in N₂O and O₂ in six subjects and desflurane in O₂ in six. Four subjects received 2.08 MAC desflurane in O₂, and six subjects received 2.08 MAC with N₂O.

For each MAC level, we attained the desired end-tidal concentration and then continued equilibration for at least 12 min before we measured EEG activity. After obtaining EEG measurements, we obtained an arterial blood sample to verify that the PaCO₂ equaled 35–40 mmHg. Spontaneous ventilation then was instituted. After a 12-min period allowed for each subject to reach a steady-state ventilatory pattern, we repeated the EEG and arterial blood gas measurements. This process was repeated with spontaneous ventilation at the three (or four, if tolerated hemodynamically) MAC levels.

After the sequence of concentrations at normocapnic and hypercapnic states, mechanical ventilation was adjusted to create a PaCO₂ of ≈25 mmHg at 1.24 MAC. During this hypocapnic test, the subject was stimulated by repetitive, 1-Hz hand clapping lasting 60 s at the subject’s head in an effort to evoke epileptiform activity. Finally, after at least 6 h of anesthesia, the 0.83 and 1.66 MAC doses with normocapnia were repeated with the initial background gas, either O₂ or N₂O/O₂, to assess any possible long-term tolerance or other instability of response related to duration of anesthesia.

EEG signals from the four-channel montage were amplified, filtered, and displayed by a Brain-Mate® system (Interspec, Ambler, PA). Input amplifiers were set to pass signals in the range of 1.0–30 Hz, and gain was set to provide a full-scale reading for 160 μV peak-to-peak. The digitized, raw EEG waveforms were displayed continuously in real time on a Macintosh SE (Apple Computer, Cupertino, CA) at the standard sweep speed of 30 mm/s throughout the protocol. These waveforms were monitored for evidence of epileptiform or other atypical activity. Two to 5 min of noise-free raw signals were recorded for off-line quantitative analysis on an analog tape recorder (model C-4, AR Vetter, Rebersburg, PA) after the period of steady-state equilibration at each dose.

Quantitative EEG (QEEG) analysis was performed with a Macintosh IIx and a “virtual” analyzer created with LabView® software (National Instruments, Austin, TX). The off-line analyzer sampled all channels at 128 Hz with 12-bit resolution and calculated the following parameters: zero crossing frequency (ZXF), median power frequency (MPF), spectral edge frequency (SEF), and burst suppression ratio (BSR). To improve noise immunity, the BSR algorithm was modified slightly to recognize suppression intervals longer than 0.5 s, rather than the original 0.24 s. To adjust the SEF empirically to reflect the presence of periods of suppression, an additional parameter, the burst-compensated SEF (BSEF), was calculated:

\[ \text{BSEF} = \text{SEF} \left(1 - \frac{\text{BSR}}{100}\right) \]

Parameters were calculated for 4-s epochs and reported as means over the entire recording interval. Longer recording intervals were chosen to compensate for doses that produced nonstationary EEG activity, such as burst suppression.

This protocol also provided an opportunity to assess the relative efficacy of the calculated QEEG parameters as monitors of anesthetic “depth”—specifically, the ability to discriminate among different concentrations of desflurane anesthesia. We assessed this with a figure of merit (FOM), which indicated the magnitude of the change in the parameter over the 0.83–1.66 MAC range as a fraction of the full scale of the parameter. The full scale range for the BSR was 100 (%) and 30 (Hz) for the other parameters.

QEEG data were compared by analysis of variance with repeated measures or two tailed t tests, as appropriate. Differences were considered significant when P < 0.05.

Results

In the awake volunteer, the EEG dominant frequency from the anterior scalp was significantly faster than that from the posterior scalp. This finding was most prominent in the MPF and less so in the ZXF and SEF (fig. 1). Induction of anesthesia eliminated any differences between QEEG parameters calculated from the frontocentral and parietooccipital leads. There were no interhemispheric

** "Nonstationary" refers to statistical instability; i.e., the quantitative EEG parameters computed during burst suppression, a nonstationary activity, vary widely from second to second. Nonstationary conditions violate many of the assumptions involved in digital signal processing.
Fig. 1. Comparison of anterior versus posterior frequency distribution during desflurane anesthesia, (FP1-C3 (a) and P3-O1 (p)). In awake subjects, there was a tendency toward higher frequencies in the anterior lead that became significant in the MPF parameter. This spatial inequality disappeared during administration of desflurane.

(right vs. left) differences. Therefore, QEEG results reported here are from FP1-C3 unless otherwise noted.

Desflurane caused a depression of cortical electrical activity (fig. 2). No epileptiform or other aberrant activity was seen at any time. With increasing anesthetic doses, background activity initially slowed and then increasingly was suppressed without further slowing. Thus, frequency-based QEEG measures (ZXF, MPF, and SEF) detected progressive slowing in the change from awake to 0.83 MAC, and further slowing at 1.24 MAC. Once burst suppression had begun (at 1.24 MAC in most subjects), the frequency content of the remaining bursts of activity did not slow further with increasing concentrations of desflurane (fig. 3), but did increase the degree of cortical suppression as characterized by the BSR and BSEF. The EEG signals were quantitatively stable less than 5 min after a change to a new end-tidal concentration.

The substitution of 60% N2O for 3% desflurane (approximately 0.45 MAC in this age group) was associated with significantly increased EEG activity (decreased burst suppression when suppression was present and increased frequency content at lower concentrations) at all same-dose (MAC) levels except 1.24 MAC.

At 1.24 MAC, changes in ventilation altered the Pco2 from 25.7 ± 0.83 mmHg during hyperventilation to 57.53 ± 1.75 mmHg (table 1) during spontaneous ventilation. These alterations in Pco2 did not alter either the frequency content (fig. 4A) or the degree of burst suppression (percentage of time the EEG showed near-isoelectricity) (fig. 4B) at 1.24 MAC.

Repetitive auditory stimuli (hand clapping) during hyperventilation at 1.24 MAC, with and without N2O, caused clearly visible middle- and long-latency evoked potentials (up to 1,000 ms), particularly when suppression of background activity was otherwise present.

The EEG at 0.83 and 1.66 MAC after an additional 6 h of exposure to desflurane demonstrated that the burst suppression phenomena was nonstationary, having a frequent tendency to appear and fade at inconstant intervals. On average, the degree of burst suppression at 1.66 MAC at the end of the study did not differ from that at the beginning (fig. 5). During desflurane in O2 the first trial yielded a mean BSR of 40.4 ± 18% and the second trial a BSR of 34.9 ± 13% (P = 0.81). In the presence of N2O, the mean BSR was initially 2.9 ± 1.3%, and during the repeated trial the BSR was 0.4 ± 0.25% (P = 0.85).

The QEEG parameters correlated to some extent with...
changes in desflurane dose (table 2). Some parameters had a larger signal change and FOM over a clinically useful range of anesthetic concentrations than did others (table 3). During desflurane in O₂, the BSR parameter had the largest FOM, indicating that the BSR provided the best discrimination between 0.85 and 1.66 MAC. The standard (uncompensated) SEF had a poor correlation with desflurane concentration; the EEG retained high-frequency activity during the intermittent bursts that occurred at the higher doses. The BSEF performed better than did the other frequency-based parameters, which did not account for the presence of burst suppression in their algorithms. During desflurane with N₂O, there was slowing with little burst suppression in the 0.83–1.66 MAC range, and therefore, the frequency-based parameters all performed with higher FOM than did the BSR.

Discussion
With increasing concentration, desflurane produces a pattern of increasing cortical depression. Desflurane and isoflurane appear to induce similar levels of cortical depression at similar MAC multiples in humans. Eger et al.² found (with a manual-measurement algorithm) electrical silence 5% of the time at 0.96 MAC isoflurane and 31% of the time at 1.46 MAC, and found complete silence at 1.96 MAC; these results suggest a curve slightly to the left of that in figure 3A. Both agents appear to preserve high-frequency EEG activity within the intermittent bursts.⁵ Moderate concentrations of enfurane, given under conditions of hypocapnia, in the presence of auditory stimulation predispose to epileptiform activity in dogs,¹⁰ swine,⁵ and humans.⁵ Like isoflurane, desflurane does not generate epileptiform activity, even with the addition of hypocapnia and auditory stimulation.

Other potent anesthetics that depress the EEG also depress the cerebral metabolic rate (CMRO₂), suggesting that desflurane may also produce a dose-related depression of CMRO₂. Lutz et al.¹¹ report a decline in CMRO₂ in dogs (from 3.4 ml·min⁻¹·100 g⁻¹ at 0.5 MAC desflurane to 2.5 ml·min⁻¹·100 g⁻¹ at 2.0 MAC) that was similar to results obtained in dogs with isoflurane.

The substitution of N₂O for 0.45 MAC desflurane increased EEG activity (and diminished BSR) at every dose level above 0.83 MAC. The amount of desflurane sub-

<table>
<thead>
<tr>
<th>Dihlurane</th>
<th>Ventilation</th>
<th>pH</th>
<th>PCO₂</th>
<th>PO₂</th>
</tr>
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<tbody>
<tr>
<td>O₂</td>
<td>Hyperventilation</td>
<td>7.57 ± 0.02</td>
<td>25.7 ± 0.83</td>
<td>492.46 ± 37.56</td>
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<td></td>
<td>Mechanical</td>
<td>7.44 ± 0.02</td>
<td>37.57 ± 1.13</td>
<td>463.58 ± 14.60</td>
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<tr>
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<td>Spontaneous</td>
<td>7.28 ± 0.02</td>
<td>57.53 ± 1.75</td>
<td>457.67 ± 15.55</td>
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<tr>
<td>N₂O</td>
<td>Hyperventilation</td>
<td>7.54 ± 0.01</td>
<td>25.83 ± 0.68</td>
<td>180.68 ± 15.81</td>
</tr>
<tr>
<td></td>
<td>Mechanical</td>
<td>7.40 ± 0.01</td>
<td>39.47 ± 1.65</td>
<td>157.27 ± 8.38</td>
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<tr>
<td></td>
<td>Spontaneous</td>
<td>7.32 ± 0.01</td>
<td>49.63 ± 2.12</td>
<td>152.30 ± 10.49</td>
</tr>
</tbody>
</table>

All values are expressed as the mean ± SE.
FIG. 5. All of the individual BSR responses of the subjects and their variations over time. Each of the 12 subjects had a set (0.83 and 1.66 MAC) of repeated measurements at least 6 h after the first measurement. The repeated measurements were done either with or without N₂O, depending on whether the individual was randomized to O₂ or N₂O in the first set of measurements. The data plotted represents the BSR at the 1.66 MAC level during normocapnea. The squares are O₂-desflurane subjects; the triangles represent those receiving N₂O as well. There was wide variance due to the nonstationary nature of burst suppression with desflurane, but there was no trend to suggest that BSR was different after a 6-h exposure to desflurane.

†† Smith NT, Hoff BH, Rampil IJ, Sasse FJ, Fleming DC: Does thiopental or N₂O disrupt the EEG during enflurane? (abstract) ANESTHESIOLOGY 51:S4, 1979

FIG. 4. At 1.24 MAC desflurane there was no difference in either (A) frequency content (as quantitated by SEF and ZXF) or (B) degree of suppression (as quantitated by BSR) due to changes in PₐCO₂ ranging from 26 (LOW) to 58 (HIGH) mmHg.
TABLE 2. Quantitative EEG Parameters: Response to Varying Concentrations of Desflurane

<table>
<thead>
<tr>
<th>Carrier</th>
<th>Dose</th>
<th>ZNF</th>
<th>BSR</th>
<th>MFF</th>
<th>SEF</th>
<th>BSEF</th>
</tr>
</thead>
<tbody>
<tr>
<td>O₂</td>
<td>0</td>
<td>4.5 ± 0.2</td>
<td>0.0 ± 0.0</td>
<td>5.1 ± 0.7</td>
<td>20.6 ± 0.9</td>
<td>20.6 ± 0.9</td>
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<tr>
<td></td>
<td>0.85</td>
<td>3.6 ± 0.1</td>
<td>0.1 ± 0.1</td>
<td>3.4 ± 0.4</td>
<td>14.4 ± 0.4</td>
<td>14.4 ± 0.4</td>
</tr>
<tr>
<td></td>
<td>1.24</td>
<td>2.8 ± 0.1</td>
<td>4.0 ± 3.7</td>
<td>1.8 ± 0.1</td>
<td>13.0 ± 0.7</td>
<td>12.4 ± 0.8</td>
</tr>
<tr>
<td></td>
<td>1.66</td>
<td>2.5 ± 0.1</td>
<td>42.6 ± 8.7</td>
<td>2.1 ± 0.2</td>
<td>14.1 ± 1.2</td>
<td>7.6 ± 1.0</td>
</tr>
<tr>
<td></td>
<td>2.0</td>
<td>2.0 ± 0.2</td>
<td>69.7 ± 19.4</td>
<td>1.8 ± 0.2</td>
<td>14.7 ± 1.6</td>
<td>4.3 ± 2.7</td>
</tr>
<tr>
<td>r²</td>
<td>0.57</td>
<td>0.55</td>
<td>0.36</td>
<td>0.25</td>
<td>0.69</td>
<td></td>
</tr>
</tbody>
</table>

| N₂O     | 0.83 | 4.2 ± 0.3 | 0.5 ± 0.2 | 4.2 ± 0.6 | 17.1 ± 0.7 | 17.0 ± 0.7 |
|         | 1.24 | 2.5 ± 0.2 | 1.1 ± 0.5 | 1.8 ± 0.2 | 10.6 ± 0.9 | 10.5 ± 0.9 |
|         | 1.66 | 2.4 ± 0.2 | 1.5 ± 0.5 | 1.4 ± 0.6 | 10.4 ± 0.8 | 10.2 ± 0.8 |
|         | 2.0  | 2.8 ± 0.6 | 32.4 ± 16.4 | 2.6 ± 0.3 | 14.5 ± 1.8 | 8.4 ± 1.7 |
| r²      | 0.29 | 0.16 | 0.20 | 0.18 | 0.45 | |

All data are expressed as the mean ± SE.
The r² values under each column refer to the correlation coefficient for a linear regression of the corresponding parameter versus desflurane concentration. In all cases, the P value (ANOVA) was <0.0003.

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References

2. Eger EI II, Stevens WC, Cromwell TH: The electroencephalogram in man anesthetized with Forane. ANESTHESIOLOGY 35:504-508, 1971
8. Rampil IJ, Matteo RS: Changes in EEG spectral edge frequency correlates with the hemodynamic response to laryngoscopy and intubation. ANESTHESIOLOGY 67:139-142, 1987