EFFECT OF PROPOFOL ON THE AUDITORY EVOKED RESPONSE AND OESOPHAGEAL CONTRACTILITY


This study had two objectives: to examine the effect of propofol anaesthesia on the auditory evoked response (AER) as part of a series of studies [1-4] to develop a technique for measuring "depth of anaesthesia", and to compare changes in the AER produced by propofol with changes in oesophageal contractility, a technique which has been claimed [5] to measure depth of anaesthesia.

Changes in contractility of the lower portion of the oesophagus have been proposed as a measure of depth of anaesthesia. The contractions studied have been of two types: spontaneous contractions (SLOC), and provoked contractions (PLOC) produced by stimulating the oesophagus; the frequency of both has been related inversely to concentration of anaesthetic administered [5]. In the absence of an absolute standard against which to compare either the AER or oesophageal contractility, we have compared these with each other.

SUMMARY

Six patients were anaesthetized with 70% nitrous oxide in oxygen supplemented by infusion of propofol 40, 80, 120, 160 and 200 μg kg⁻¹ min⁻¹ sequentially in successive 10-min periods. Auditory evoked response (AER) and lower oesophageal contractility (LOC) were monitored. The AER findings were consistent with those noted in previous studies of i.v. agents. Early cortical waves showed attenuation of Pa and Nb amplitude (P < 0.01) and increase in Pa and Nb latency (P < 0.01; P < 0.05) with increasing blood concentrations of propofol. Brainstem waves were not affected significantly. LOC, provoked and spontaneous, showed no consistent relationship with blood concentration of propofol. The two variables AER and LOC were not related.

PATIENTS AND METHODS

Patients and anaesthesia

Six patients aged 18-45 yr gave informed consent to the study, which was approved by Harrow District Ethics Committee and the Committee on Safety of Medicines. Premedication with morphine 10 mg and atropine 0.6 mg i.m. was followed by induction of anaesthesia with thiopentone 2-4 mg kg⁻¹ i.v. The trachea was intubated following administration of pancuronium 0.1 mg kg⁻¹ i.v. and the lungs ventilated with 70% nitrous oxide in oxygen. Seven to 10 min after induction, propofol was infused i.v. in five equal 10-min steps, starting at 40 μg kg⁻¹ min⁻¹ and with a final rate of 200 μg kg⁻¹ min⁻¹. In two patients (P1 and P5) in whom there was a delay between the end of the study and the beginning of surgery, the recovery of the AER was monitored while the patient's lungs were ventilated with 70% nitrous oxide in oxygen.

Ventilation was adjusted to maintain the end tidal carbon dioxide concentration (Hewlett-Packard 47210A infra-red analyser) within the range 4.5-5.5 kPa. Body temperature was monitored using a thermistor placed in the oesophagus...
at the level of the aortic arch. Systemic arterial pressure and heart rate were recorded at 5–10 min intervals.

Auditory evoked response

The technique was essentially the same as that described previously [6], except for the use of purpose built EEG amplifiers with the same amplification and filter characteristics. Averages (n = 2048) of the auditory evoked response to click stimulation at 6 Hz were obtained before anaesthesia, after induction of anaesthesia before the start of the infusion of propofol, and at end of each infusion period. To monitor recovery after discontinuation of the infusion, AER responses were obtained over 3-min epochs.

Oesophageal contractions

Following intubation of the trachea, the AN-TEC oesophageal monitor was used to record oesophageal contractions as described by Evans and White [7]. The oesophageal pressure probe was introduced into the lower one-third of the oesophagus (probe tip 35 cm from the lips). Spontaneous lower oesophageal contractions (SLOC) and provoked lower oesophageal contractions (PLOC) are identical in appearance, the latter distinguished from the former by occurring after a pressure stimulus set to occur automatically.

Anaesthetic concentration

Venous blood samples were taken from the arm opposite to that receiving the infusion, just before starting the propofol and in the 6th, 8th and 10th min of each infusion period. In two patients in whom recovery was monitored, a sample was taken in the middle and at the end of this period. Blood concentrations of propofol were measured by Dr E. Douglas of I.C.I. according to the method of Plummer [8].

Analysis of data

We examined brainstem waves (I, III and V latencies; I–III, I–V and III–V interpeak intervals; III and V amplitude) and early cortical waves (Pa and Nb latencies; Pa and Nb amplitudes).

AER variables for each patient were plotted against time (midpoint of the averaging period) and against propofol concentration (mean of the blood samples obtained in the 6th, 8th and 10th min of each infusion period). The datum point following induction of anaesthesia just before the addition of the test agent was given a time or a concentration of zero. The averaged AER were recorded over the final 5.7 min of each 10-min period. Regression analysis was used to calculate a slope for each patient, and analysis of variance was carried out on the slopes to compare the effect of propofol with that of other drugs and saline from previous studies [1–4] and to test for dose relationships. (Data from these studies were reanalysed to include the post-induction data point.)

Oesophageal contraction variables examined were: mean height (mm Hg) of provoked oesophageal contractions (PLOC) and frequency of spontaneous oesophageal contractions (SLOC). For PLOC, the values corresponding to the AER sample period were averaged to give the mean PLOC height, and for the SLOC they were expressed as frequency per 5 min. Mean PLOC height and SLOC frequency were plotted against blood concentration of propofol and the mean slopes of these variables tested for a significant difference from zero.

The Pa and Nb latencies and amplitudes were plotted also against mean PLOC height and SLOC frequency and the significance of the mean slopes tested to see if these variables were related.

RESULTS

Propofol and AER

Brainstem response

Propofol resembled the other two i.v. agents, etomidate and Althesin, in that the mean slopes of the brainstem latencies and interpeak intervals against time were not significantly different from saline at the P < 0.05 level (table I). On the other hand, the inhalation agents had effects consistently different from those of saline on the III and V latencies, and interpeak intervals.

Early cortical response

With increasing blood concentrations of propofol, there were progressive increases in latency and reductions in amplitude of waves Pa and Nb similar to those observed with halothane, enflurane, isoflurane, etomidate and Althesin, but not in the patients given saline (fig. 1).

As with the other anaesthetic agents, the changes in Pa and Nb latency and amplitude reversed when the propofol infusion was stopped. Figure 2 shows the early cortical AER in one
Table 1. Brainstem latency and interpeak interval regressions against time. The pooled estimate of the between-patient SD of the variable was derived from an analysis of variance and used for the comparison between anaesthetic agents and saline. Means significantly different from that of saline: *P < 0.05; **P < 0.01; ***P < 0.001

<table>
<thead>
<tr>
<th></th>
<th>Latencies</th>
<th>Interpeak intervals</th>
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<tbody>
<tr>
<td></td>
<td>n</td>
<td>I</td>
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<tr>
<td>Mean slopes (ms x 10) min⁻¹</td>
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<td></td>
</tr>
<tr>
<td>Halothane</td>
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<tr>
<td>Enflurane</td>
<td>6</td>
<td>0.02</td>
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<tr>
<td>Isoflurane</td>
<td>6</td>
<td>0.01</td>
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<tr>
<td>Etomidate</td>
<td>7</td>
<td>0.02</td>
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<tr>
<td>Althesin</td>
<td>5</td>
<td>0.00</td>
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<tr>
<td>Propofol</td>
<td>6</td>
<td>0.01</td>
</tr>
<tr>
<td>Saline</td>
<td>7</td>
<td>0.02</td>
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<tr>
<td>Pooled estimate of SD (ms x 10) min⁻¹</td>
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<td></td>
</tr>
<tr>
<td>All groups</td>
<td>43</td>
<td>0.024</td>
</tr>
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Fig. 1. Early cortical responses in (A) patient P4 given propofol and (A) patient S6 given saline infusions. At the concentration or infusion rate labelled zero, the anaesthesia was maintained on 70% nitrous oxide in oxygen. Vertical bar = 0.5 μV.

Fig. 2. Early cortical responses in patient P1, in whom the infusion rate was discontinued (patient receiving 70% nitrous oxide in oxygen) and recovery of the AER was monitored. At similar blood concentrations of propofol (0.56 and 0.69 μg ml⁻¹) the amplitudes and latencies of the early cortical waves are similar. Vertical bar = 0.5 μV.

Patient at similar blood concentrations of propofol, but separated by a period of 57 min.

In the statistical analyses, log transformations of the early cortical latencies and amplitudes were used on the data for propofol and data published previously [1–4]. In the tables and figures the data have been transformed back to the original units. Proportional change and 95% confidence limits are given instead of means and SEM.

Comparisons with saline. For all six general anaesthetics the mean slopes of all early cortical variables against time (Table II) were significantly different from the saline group (P < 0.05), with the exception of the reduction in Nb amplitude by halothane (P = 0.12).
Table II. Early cortical latency and amplitude regressions against time (mean slopes and 95% confidence limits (% change min⁻¹)). The pooled estimate of the between-patient SD of the variable was derived from an analysis of variance and used for the comparison between anaesthetic agents and saline. Means significantly different from that of saline: *P < 0.05; **P < 0.01; ***P < 0.001

<table>
<thead>
<tr>
<th>Anaesthetic</th>
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<th>Nb Latencies</th>
<th>Pa Interpeak intervals</th>
<th>Nb Interpeak intervals</th>
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<tr>
<td>Halothane</td>
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<td>7** (4 to 11)</td>
<td>8** (4 to 13)</td>
<td>-25* (-16 to -33)</td>
<td>-20 (-10 to -29)</td>
</tr>
<tr>
<td>Enflurane</td>
<td>6</td>
<td>18*** (14 to 22)</td>
<td>14*** (9 to 19)</td>
<td>-43*** (-37 to -49)</td>
<td>-36*** (-28 to -43)</td>
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<tr>
<td>Isoflurane</td>
<td>6</td>
<td>20*** (16 to 23)</td>
<td>23*** (18 to 28)</td>
<td>-47*** (-40 to -52)</td>
<td>-45*** (-38 to -51)</td>
</tr>
<tr>
<td>Etomidate</td>
<td>7</td>
<td>10*** (7 to 14)</td>
<td>10*** (6 to 15)</td>
<td>-25** (-17 to -32)</td>
<td>-27** (-19 to -35)</td>
</tr>
<tr>
<td>Althesin</td>
<td>5</td>
<td>8** (4 to 12)</td>
<td>9** (4 to 14)</td>
<td>-31** (-22 to -39)</td>
<td>-36*** (-27 to -44)</td>
</tr>
<tr>
<td>Propofol</td>
<td>6</td>
<td>6* (2 to 9)</td>
<td>9** (5 to 14)</td>
<td>-26* (-17 to -33)</td>
<td>-22* (-13 to -31)</td>
</tr>
<tr>
<td>Saline</td>
<td>7</td>
<td>1 (-4 to 3)</td>
<td>0 (-4 to 3)</td>
<td>-9 (1 to -18)</td>
<td>-9 (1 to -19)</td>
</tr>
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</table>

Dose relationships. The changes with propofol, as with the other anaesthetic agents, were related linearly to concentration (fig. 3). The mean slopes of Pa and Nb latency and amplitude against concentration were significantly different from zero ($P < 0.05$) in all cases, except for the effects of Althesin on Nb latency (table III). In figure 3 and table III the propofol concentration is expressed in $\text{ED}_{50}$ units, which are units of equipotency (their derivation is discussed later). This does not affect the significance of the difference of the mean slope from zero.

Comparison of anaesthetics. On the basis of these derived $\text{ED}_{50}$ estimates, an attempt was made to compare the effect of the six general anaesthetics on the early cortical variables. There appeared to be large differences between the slopes of the inhalation and i.v. agents in table III. However, it is not statistically valid to compare a mean of 29%, confidence interval 14–45%, with a mean of 896%, confidence interval −16 to 7469%. These quantitative comparisons were therefore not pursued. We discuss problems of estimating equipotency later.

Propofol and Oesophageal Contractions

Provoked lower oesophageal contractions (PLOC)

The PLOC data (log transformed) plotted against propofol concentration are shown in figure 4. In three patients (P1, P2, P4) at low blood concentrations of propofol, PLOC decreased from 19–34 mm Hg to less than 10 mm Hg, at which value it remained. In another patient (P3) PLOC fluctuated below 10 mm Hg throughout the study.
TABLE III. Early cortical latency and amplitude regressions against concentration (mean slopes and 95\% confidence limits (° change ED_{50} units^{-1})). An ED_{50} unit is equivalent to end-tidal concentrations of 1.68\% enflurane; 0.75\% halothane and 1.15\% isoflurane; blood propofol 9.76 μg ml^{-1}; plasma alphaxalone 11.23 μg ml^{-1} and serum etomidate 2.35 μg ml^{-1}. Means significantly different from zero (SEM for individual drugs were used to test this): *P < 0.05; **P < 0.01; ***P < 0.001

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<thead>
<tr>
<th></th>
<th>n</th>
<th>Pa</th>
<th>Nb</th>
<th>Amplitudes</th>
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<td>6</td>
<td>24**</td>
<td>29**</td>
<td>-59**</td>
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<td>6</td>
<td>62**</td>
<td>45**</td>
<td>-81**</td>
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<tr>
<td>Isoflurane</td>
<td>5</td>
<td>58**</td>
<td>60**</td>
<td>-76**</td>
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<td>-100**</td>
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<tr>
<td>Etomidate</td>
<td>7</td>
<td>387**</td>
<td>402*</td>
<td>-98**</td>
<td>-99**</td>
<td>-100**</td>
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<tr>
<td>Althesin</td>
<td>5</td>
<td>560***</td>
<td>896*</td>
<td>-100**</td>
<td>-100**</td>
<td>-99**</td>
</tr>
<tr>
<td>Propofol</td>
<td>6</td>
<td>80**</td>
<td>139**</td>
<td>96**</td>
<td>94**</td>
<td>-99**</td>
</tr>
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</table>

In the other two patients (P5 and P6) the reduction in PLOC was related more linearly to blood concentration of propofol. Because of the variations between patients, the mean slope for the group was not significantly different from zero at P < 0.05.

Spontaneous lower oesophageal contractions (SLOC)

Only three of the 34 data points were above the background noise level of 4 contractions per 5 min. These values were 12, 14 and 25 SLOC per 5 min, respectively. The 25 contractions were associated with a large dose of propofol. Four patients showed no SLOC throughout the entire study. A generalized statement about the group data cannot, therefore, be made.

AER and Oesophageal Contractions

There was no consistent relationship between AER variables and oesophageal contractions. The relationship appeared to be linear in only two of the patients, P1 and P6.

Body Temperature and Arterial Pressure

Small decreases in body temperature (max. 0.5 °C) occurred in some, but not all, patients. There was an inverse relationship between systolic arterial pressure and concentration of propofol. The systolic pressure never decreased to less than 80 mm Hg.

DISCUSSION

Propofol had effects on the early cortical AER similar to those of halothane, enflurane [1], isoflurane [4], Althesin [3] and etomidate [2]. As with these agents, increasing concentrations of propofol reduced amplitudes and increased latencies of waves Pa and Nb, and the changes were reversible. These changes in the early cortical variables were related linearly to concentration, so the slopes against concentration in ED_{50} units could be compared.

For the inhalation agents, ED_{50} was taken as the MAC value determined in air (0.75\% halothane, 1.68\% enflurane and 1.15\% isoflurane [9]). The MAC values are derived from the end-tidal concentration of an inhalation agent—a good estimate of the blood concentration. For the i.v. agents, the minimum infusion rate (MIR) that prevents movement in response to surgical incision is an attempt to extend the MAC concept.
However, an administered infusion rate bears no close relationship with blood concentration. To reduce pharmacokinetic variability we have correlated AER changes with blood concentration rather than infusion rate, unlike previous reports [10, 11]. The mean blood concentrations at each MIR were used as ED$_{50}$ values in this study. Assumptions have to be made to predict ED$_{50}$ from the available data to allow for the effects of supplementary drugs such as nitrous oxide, morphine and fentanyl given during the studies estimating MIR [12–15]. A correction of 0.83 MAC was applied to the ED$_{50}$ values for nitrous oxide with morphine premedication [12, 16, 17] or equivalent combination of drugs.

Quantitative comparisons of the effects of different agents (table III) revealed such large differences between the inhalation and i.v. anaesthetics as to make the conversion factors suspect. For example, the predicted change of a nine-fold increase in latency with Althesin are far in excess of those ever seen in practice. This highlights the problem of extrapolating outside the clinical concentration range. The greatest blood concentration of propofol reached in the study was 4.49 µg ml$^{-1}$, and that for enfurane 3.14%, at which concentrations these drugs produced similar changes. However, when the ED$_{50}$ conversions were applied (giving 0.46 ED$_{50}$ units for propofol and 1.87 for enfurane), the predicted differential effects on AER were large. Drugs such as etomidate, Althesin and propofol have a high MAC/ED$_{50}$ value, probably because they have low analgesic properties, and the MAC endpoint reflects analgesia as much as hypnosis. Our speculation is, therefore, that the AER reflects the hypnotic component of an anaesthetic drug. Clinical experience with propofol has shown that, while moderate concentrations produce sleep and preclude recall, movement in response to painful stimulus cannot be prevented reliably even when using the greatest recommended dose. Studies to determine MAC using propofol have used drugs with analgesic properties to achieve this level [14].

In contrast with inhalation agents, the effects of propofol and other i.v. agents on brainstem variables were not significantly different from those of saline. Inhalation agents caused increases in latency of waves III, V and III–V interpeak interval related linearly to their end-tidal concentrations.

Oesophageal contractility was not related to concentration of propofol in any obvious way. The response from some patients never registered above background noise for either SLOC frequency or PLOC height throughout the entire study. Of the two variables, SLOC frequency showed the least appropriate changes, showing high readings for high concentrations of propofol and low readings when there was no propofol. The reverse would have been expected.

Our anaesthetic was not “clean” propofol, but consisted of nitrous oxide and residual effects of morphine and thiopentone, and we acknowledge that this may not be the ideal procedure for evaluating the effect of propofol on LOC. However, this was not our main aim; we wished primarily to look at the effect on the AER of propofol using a procedure similar to that used for the other anaesthetics studied. This involved giving morphine, atropine, thiopentone and nitrous oxide. These drugs are used so frequently in anaesthetic practice that any technique would have to be sufficiently robust to withstand interference from them.

Although boluses of i.v. atropine may cause complete suppression of LOC (J. M. Evans, personal communication), atropine given i.m. as a premedicant, does not affect LOC so profoundly. Although the absolute value of LOC is diminished, the available data suggest that the graded reduction in contractility with increasing anaesthetic concentration is still seen. To our knowledge, atropine does not affect AER. If it causes such problems for the LOC technique, this is clearly a disadvantage. No i.v. boluses of atropine were given during this study.

Other workers have found LOC rather variable as a clinical monitor of “depth of anaesthesia”. Aitkenhead, Lin and Thomas [18] concluded that SLOC frequency and PLOC amplitude are related to clinical signs of light anaesthesia, but that neither is, by itself, an accurate predictor of inadequate anaesthesia. Erikson, Foss and Kuni [19] found no advantage of LOC over heart rate–arterial pressure trends or agent concentration with isoflurane anaesthesia. Our preliminary use of the technique has led us to the same opinion.

In conclusion, our experience of the lower oesophageal contractility monitor leads us to believe that this technique would have limited use as a clinical monitor of depth of anaesthesia. We are also firmly of the opinion that monitoring brainstem AER is not reliable, as not all general anaesthetics produce changes in this response. We
believe that the early cortical response remains robust, as it clearly measures an aspect of depth of anaesthesia. It is affected in the same way by all the general anaesthetics that we have studied, although the quantitative differences based on conventional measures of potency between the general anaesthetic agents requires explanation.

REFERENCES