EARLY CORTICAL AUDITORY EVOKED RESPONSE IN Anaesthesia: COMPARISON OF THE EFFECTS OF NITROUS OXIDE AND ISOFLURANE

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Previous studies on depth of anaesthesia have shown graded changes in the auditory evoked response (AER) in patients anaesthetized with increasing concentrations of volatile anaesthetic agents [1,2]. In these studies the amplitudes of the early cortical waves, Pa and Nb, decreased progressively as the concentrations of halothane, enflurane and isoflurane were increased. However, when observed several minutes after induction of anaesthesia and before the administration of the volatile agent, the amplitudes of these early cortical waves appeared frequently to exceed their pre-anaesthetic values. In this period, anaesthesia was provided solely by nitrous oxide and the declining concentration of the induction agent, thiopentone.

From these data it is not possible to differentiate between the effects of nitrous oxide alone, which could possibly have had an excitatory effect, and those effects produced by the potentially stressful sequence (induction of anaesthesia and tracheal intubation) that preceded it. Recent studies have shown that the depression of the early cortical AER by anaesthetic agents may be reversed partially by the stimulus of surgery [3].

We have conducted a cross-over study to examine the effects on these AER waves of the period immediately after induction and tracheal intubation in patients anaesthetized with equal MAC (minimal alveolar concentration) fractions of either nitrous oxide or isoflurane.

SUMMARY

Previous studies showing graded changes in the early cortical waves Pa and Nb of the auditory evoked response (AER) with increasing concentration of volatile anaesthetic agents demonstrated high amplitudes of these waves in the period immediately following induction of anaesthesia and tracheal intubation, when the patient breathed nitrous oxide alone. These high amplitude waves were not consistent with extrapolation of the data or observations of patients under steady-state nitrous oxide anaesthesia. In order to discriminate between effects in the period immediately following induction of anaesthesia and tracheal intubation, and effects caused by nitrous oxide alone, a randomized cross-over study was performed. Eight patients breathed either nitrous oxide or isoflurane at 0.6 MAC for three consecutive 10-min periods following intubation and before surgery. The amplitudes of Pa and Nb were significantly less for isoflurane with respect to the same MAC fraction of nitrous oxide in all periods, but for both agents the amplitudes were significantly greater in the 10 min following intubation than in subsequent periods, presumably as a result of stimulation.

METHODS

Patients and anaesthesia

We studied eight patients (ages 38–49 yr; ASA I or II) undergoing major general or gynaecological abdominal surgery. The patients consented to the measurement of AER during 30 min of anaesthesia before surgery; the study was approved by the hospital Ethics Committee.
Table I. Experimental design for within subject comparison between nitrous oxide (N₂O) and isoflurane (ISO). Two patients in each sequence. Periods were consecutive, and of 10 min duration

<table>
<thead>
<tr>
<th>Sequence</th>
<th>Period 1</th>
<th>Period 2</th>
<th>Period 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ISO</td>
<td>N₂O</td>
<td>N₂O</td>
</tr>
<tr>
<td>2</td>
<td>N₂O</td>
<td>ISO</td>
<td>N₂O</td>
</tr>
<tr>
<td>3</td>
<td>ISO</td>
<td>N₂O</td>
<td>ISO</td>
</tr>
<tr>
<td>4</td>
<td>N₂O</td>
<td>ISO</td>
<td>ISO</td>
</tr>
</tbody>
</table>

Each patient was premedicated with morphine 10–15 mg and atropine 0.6 mg, or papaveretum 15–20 mg and hyoscine 0.3–0.4 mg, i.m. 1 h before induction of anaesthesia with thiopentone 2–4 mg kg⁻¹. Intubation of the trachea was facilitated by either pancuronium or vecuronium 0.1 mg kg⁻¹ and mechanical ventilation was adjusted to maintain an end-tidal Pco₂ of 4.5–5.0 kPa (Hewlett-Packard 47210A capnometer). Following tracheal intubation, the inspired gas mixture was adjusted to produce the required end-tidal concentrations (60–65% nitrous oxide or 0.65–0.75% isoflurane), as measured by mass spectrometer (Medishield MS2, calibrated by volumetrically prepared gas samples). These concentrations were chosen to give a fraction of approximately 0.6 MAC [4]. The anaesthetic administered was changed in each of the eight patients in three consecutive 10-min periods randomized as shown in table I.

Overpressure was used to produce rapidly the required end-tidal concentrations of the chosen agent; within 5 min, it was possible to have both stable end-tidal values and residual concentrations of the previous agent less than 5% of their original value.

Systemic arterial pressure and heart rate were recorded every 2.5 min throughout the procedure using a Datascopc automatic recorder. Nasopharyngeal temperature was recorded after tracheal intubation, and at the end of the study period.

Clinical assessment of the adequacy of anaesthesia was carried out during the study by an anaesthetist (not participating in the study) who supervised the patient. After surgery, patients were seen by this anaesthetist, who noted any volunteered recall of events during the procedure.

Recording the auditory evoked response

The technique has been described in detail previously [5]. In the present study a purpose-built EEG amplifier was used in place of the modified Specialized Laboratory Equipment 10/8 polygraph. The gain and filter characteristics were the same (gain 100 dB; frequency response 25–3600 Hz). Clicks (75 dB above the average auditory threshold) were administered binaurally through headphones at a rate of 6 per second. The EEG was recorded using silver-silver chloride electrodes on the vertex and inion and was amplified and stored on an FM tape recorder. The AER was analysed off-line using a Datalab DL 4000 averager, to display the average of the response to 2048 clicks, during the last 5.7 min of each period when the end-tidal values were stable. For the early cortical waves Pa and Nb, latency and amplitude were measured. The nomenclature of these waves has been discussed previously [5].

Statistical analysis

Analysis of variance was used to compare the agents used and the periods during which the agents were administered, and to determine if there was an interaction between the effect of the drug and the period in which it was given. Statistical significance was assigned at the 5% level.

RESULTS

Auditory evoked response (table II)

Nitrous oxide v. isoflurane. The effect of one sequence of administration is shown in figure 1. The change from nitrous oxide to isoflurane produced a marked reduction in amplitude and increased in latency of the early cortical waves, Pa and Nb. These changes were reversed partially by the subsequent re-administration of nitrous oxide.

Analysis of the results for all eight patients showed large and significant decreases in the amplitude of the early cortical waves Pa (P < 0.001) and Nb (P = 0.003) for isoflurane compared with nitrous oxide, irrespective of the period administered. Latencies for both waves were increased when the patients received isoflurane; the change for Pa was significant (P < 0.05).

The effect of period. The amplitudes of waves Pa and Nb were significantly greater for both agents in the initial period immediately after tracheal intubation, compared with the two subsequent periods. The latencies were not affected signifi-
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...cantly by the period. There were no significant interactions between drug and period.

The major effects were on the amplitudes of Pa and Nb. These are seen for one patient in figure 1 and are illustrated for the complete study in figure 2 for Pa amplitude, showing the consistently greater amplitude depression with 0.6 MAC isoflurane than with nitrous oxide irrespective of period, and the greater amplitudes seen in the first period, following tracheal intubation.

Cardiovascular variables

Arterial pressure and heart rate decreased significantly following the initial period, as would be expected in the absence of surgical stimulation. Systolic arterial pressure was slightly but significantly lower \((P < 0.001)\), and heart rate higher \((P = 0.02)\) in association with the administration of isoflurane compared with nitrous oxide.

In all patients temperatures remained within the range 36.0–37.5 °C during the period of investigation.

The patients appeared to be anaesthetized adequately during the period of the study (without any other stimulation), and no patient volunteered recall of any events during anaesthesia.

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**Fig. 1.** Early cortical AER recordings in one patient, showing the progression from nitrous oxide (\(N_2O\)) anaesthesia following induction and intubation to isoflurane (ISO), and back to nitrous oxide.

**Fig. 2.** The amplitudes of the early cortical AER wave Pa (SEM bars based on the pooled within-subject residual error term in the analysis of variance), for each of three consecutive 10-min periods following tracheal intubation, in eight patients receiving isoflurane (ISO) or nitrous oxide (\(N_2O\)).

**Table II. Analysis for four AER variables with respect to period (see table I) and drug (nitrous oxide \((N_2O)\) or isoflurane (ISO)).** Negative values represent reductions of latency or amplitude when going from the first to subsequent periods, or when changing from isoflurane to nitrous oxide.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Period 1 v. 2 and 3</th>
<th>Drug: ISO v. (N_2O)</th>
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<tbody>
<tr>
<td>Latency (ms)</td>
<td>Mean change</td>
<td>SEM</td>
</tr>
<tr>
<td>Pa</td>
<td>4.88</td>
<td>2.43</td>
</tr>
<tr>
<td>Nb</td>
<td>7.00</td>
<td>3.79</td>
</tr>
<tr>
<td>Amplitude ((\mu V))</td>
<td>Mean change</td>
<td>SEM</td>
</tr>
<tr>
<td>Pa</td>
<td>-0.37</td>
<td>0.11</td>
</tr>
<tr>
<td>Nb</td>
<td>-0.41</td>
<td>0.10</td>
</tr>
</tbody>
</table>
DISCUSSION

The results show that nitrous oxide has a quantitatively different effect on the auditory evoked response from that of isoflurane when each is administered at 0.6 MAC. In particular, reductions in amplitude and increases in latency of the early cortical waves Pa and Nb in both periods 2 and 3 compared with period 1, were significantly less with nitrous oxide. For both agents the early cortical amplitudes were greater in period 1 (the 10 min following induction of anaesthesia and intubation of the trachea) than in the subsequent 20 min when the responses remained lower and stable, even though the end-tidal concentrations of the anaesthetic agents were the same in all three periods. The combination of both the effects demonstrated—of period, and of nitrous oxide—may explain the initially high Pa and Nb amplitudes seen in previous studies.

The advantage of the design of this study, using three periods rather than the more usual two periods for comparison of the two agents, was that interaction between drugs and periods could be tested against within-subject variability, rather than between-subject variability, which is usually much greater [6]. Using this design, it was possible to conduct the necessary within-patient crossover, during the 30 min of anaesthesia time before the start of surgery. Thirty minutes is the maximum extension time for anaesthesia research permitted by the hospital Ethics Committee.

In both the second and third periods, the degree of depression of amplitude of Pa and Nb in this study was similar to that in anaesthetized patients in previous studies [1, 2], in which combinations of various volatile agents and nitrous oxide were used. We chose to compare nitrous oxide with isoflurane, because earlier studies have shown that the effects of the various volatile agents on the early cortical AER were similar and isoflurane, unlike halothane, could be given safely to all patients. However, in this present study, isoflurane at 0.6 MAC was exerting a greater effect than the equivalent MAC combination (nitrous oxide plus isoflurane) in the previous study [2]. It is interesting to note that, in order to achieve the required end-tidal isoflurane concentrations in this study, inspired concentrations of at least twice the end-tidal value were needed throughout the 10- or 20-min periods. We should question, therefore, the assumption of McMenemin and Parbrook [7] that the alveolar concentration should equal 60% of the inspired concentration after 20 min, and would recommend rapid response end-tidal gas analysis for studies of this type.

The effect of nitrous oxide on the auditory evoked responses has been studied extensively. Lader and Norris [8] demonstrated, in man, reductions in the amplitude of the AER by inspired concentrations as low as 12%. More recent work has demonstrated graded changes in AER amplitudes, with various concentrations up to 50% [9, 10].

The technical difficulties of recording the early cortical AER in the operating theatre [11] have ensured that it has not been studied extensively in relation to the inhalation anaesthetic agents. However, several studies [1-3, 12, 13] have demonstrated that it shows promise as a monitor because significant changes are seen in response to increasing concentrations of both inhalation and i.v. anaesthetic agents.

With the exception of the determination of MAC values in man, very few studies have been performed on volatile anaesthetic agents without the use of nitrous oxide as a carrier gas. However, we have shown that equivalent MAC fractions of nitrous oxide and isoflurane are not equipotent as indicated by the AER. This may cast some doubt on the current practice of adding MAC fractions to determine the potency of a mixture of volatile agent and nitrous oxide.

There is no reason to suppose that the dose-response curves of the AER with volatile anaesthetic agents should be similar. Our results support the comments of Eger [14] on the work of Frumin [15] and others, suggesting that the relative anaesthetic potency of nitrous oxide in clinical concentrations, from its MAC-awake value, was lower than that expected by comparison with other agents. The anomalous properties of nitrous oxide may result from both sympathetic activation, and the high analgesic component of the drug's activity.

Estimations of MAC depend on the resultant of both hypnotic and analgesic activities in response to surgical stimulus. In this study, the patients were not stimulated surgically, and only the hypnotic effects of the two drugs were tested. Thus our results may be explained by the hypothesis that we may have compared a drug good with analgesic but weak hypnotic properties against one with poor analgesic but good hypnotic actions. Further studies are necessary to demon-
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strate if the early cortical AER amplitude depression is solely a measure of hypnosis during anaesthesia.

REFERENCES