COMPARISON OF THE EFFECTS OF SUBANAESTHETIC CONCENTRATIONS OF ISOFLURANE OR NITROUS OXIDE IN VOLUNTEERS

I. M. McMENEMIN AND G. D. PARBROOK

Although nitrous oxide is a useful sedative when used in subanaesthetic concentrations, its specific effects on vitamin B₁₂ metabolism and amino acids [1, 2] appear to account for the toxicity to patients associated with its prolonged use. There is also evidence that this toxicity extends to dental staff who regularly administer nitrous oxide [3, 4]. Of alternative agents, subanaesthetic concentrations of trichloroethylene and methoxyflurane have proved less satisfactory because of slowness of uptake and excretion. Isoflurane has a rapid uptake and excretion [5] and should give a controllable level of effect with rapid recovery after use in subanaesthetic concentrations. Furthermore, it undergoes minimal metabolism [5] and long-term use is associated with few after-effects [6] and a lack of toxicity [7, 8]. Consequently, sedation with isoflurane may be expected to be safer than that provided by nitrous oxide, and studies by McLeod and his colleagues [9] have demonstrated the efficacy of isoflurane in patients in labour.

In view of these factors, it was decided to design a trial which compared subanaesthetic concentrations of isoflurane and nitrous oxide in volunteers. Because dentistry appeared one potential field for the clinical use of subanaesthetic concentrations of the agent and since, in our experience, the typical duration of inhalation sedation in dentistry is 20 min, this was chosen as the duration of the inhalation of the agent. For the purposes of the trial, a fixed concentration of 25% nitrous oxide was selected, because this is one which gives proven analgesia and sedation with few side-effects [10, 11]. On the basis of standard minimum alveolar concentrations for anaesthesia, 25% nitrous oxide would be equipotent with 0.3% isoflurane. However, the slower uptake of isoflurane would result in alveolar concentration reaching 60% of inspired concentration at the end of 20 min as opposed to 85% in the case of nitrous oxide. For the purposes of the trial, therefore, an inspired concentration of 0.4% isoflurane was chosen.

SUMMARY

A cross-over trial was performed in 12 volunteers to compare the relative potency of 25% nitrous oxide and 0.4% isoflurane when breathed for a period of 20 min. Oxygen was used as a control. The effects were observed for 35 min after drug administration. Choice reaction time, ability to tap two areas on a board and ability to perform mathematical problems were significantly impaired when inhaling nitrous oxide, the maximum effect being obtained within 5 min. With isoflurane, the effects were significantly greater than with nitrous oxide. The effect obtained after 15 min inhalation was greater than that at 5 min. Tests returned promptly to the base line after the discontinuation of the test agent. Subjective assessments were made using a series of eight visual analogue scales. Results of the scales represented by physical and mental sedation indicated that 0.4% isoflurane was more potent than 25% nitrous oxide. Significant effects were detected up to 15 min after the inhalation of the agent was stopped. Subanaesthetic concentrations of isoflurane warrant further study in patients undergoing dental treatment in which a rapid recovery from sedation is important.
SUBJECFS, MATERIALS AND METHODS

Subjects

Twelve members of the anaesthetic department (7 male) (age range 20–58 yr) volunteered for the study. All were healthy and were taking no medication. Each had the nature of the study explained.

Procedure

Each subject took part in three test sessions, receiving during each 100% oxygen, 25% nitrous oxide or 0.4% isoflurane (the last two in oxygen). Before participating in the formal sessions, each subject was familiarized with the test and gas administration apparatus. Before each session, subjects had refrained from alcohol and coffee for 12 h, and had had a normal night’s sleep.

Each session comprised eight series of tests. All sessions took place in the morning, either early or late. Each subject was tested by the same individual and at the same time of day as their previous tests. Each series of tests lasted about 5 min. At 15 and 5 min before the administration of the inhalation agent, two test series were performed, between which a test of mask fitness was obtained. At time 0, the mask was positioned and the appropriate mixture given. A small quantity of strong perfume spray was added to the reservoir bag and connecting tubing with the aim of masking the odour of the vapour. The concentration of isoflurane was increased step-wise from 0.2 to 0.3 to 0.4% over 1 min. Administration was for 20 min, series of measurements being obtained at 5 and 15 min. Thereafter, the mask was removed and the subject allowed to recover, series of assessments being performed at 25, 35, 45 and 55 min. The order of tests is summarized in table I.

The order of the administration of the inhalation agent was randomized from the six pairs of possible combinations available from three gases. Neither the subject nor the tester was aware of which gas was being given, this being known only to the anaesthetist giving the mixture (I.M.M. or G.D.P.).

Testing apparatus

Each series of assessments consisted of four tests which were performed in the following order:

Visual analogue scales. Eight different scales were used, the subject being given a sheet of paper on which eight 100-mm lines were drawn with the extremes of each dimension shown at either end. The dimensions chosen are shown in table II and fall into the categories of mental sedation (lines 1 and 2), physical sedation (3 and 4), tranquillity (5 and 6) and mood (7 and 8), as described by Norris [12]. The order of lines on each page was assigned randomly. Subjects were instructed that the terms at the ends of the lines were extremes of feelings and that they should work through each line and place a perpendicular mark—which represented their feelings at that time. The distance from that mark to the left-hand (lines 2, 4, 7 and 8) or right-hand (lines 1, 3, 5 and 6) end of each line was measured in millimetres and recorded.

Choice reaction time. A board similar to that used by Smith and Shirley [13], with 10 lights and corresponding buttons was presented to the subject (fig. 1). From the ready position (central button), the time taken for the subject to move to the button corresponding to whichever light was illuminated by the tester was measured electronically. The tester’s choice of light was as-

<table>
<thead>
<tr>
<th>Time from start of inhalation (min)</th>
<th>Procedure</th>
</tr>
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<tbody>
<tr>
<td>-15</td>
<td>1st baseline test</td>
</tr>
<tr>
<td>-10</td>
<td>Mask fit check</td>
</tr>
<tr>
<td>-5</td>
<td>2nd baseline check</td>
</tr>
<tr>
<td>0</td>
<td>Start inhalation of gas mixture</td>
</tr>
<tr>
<td>5</td>
<td>1st test during inhalation</td>
</tr>
<tr>
<td>15</td>
<td>2nd test during inhalation</td>
</tr>
<tr>
<td>20</td>
<td>Stop inhalation of gas</td>
</tr>
<tr>
<td>25</td>
<td>1st test in recovery phase</td>
</tr>
<tr>
<td>35</td>
<td>2nd test in recovery phase</td>
</tr>
<tr>
<td>45</td>
<td>3rd test in recovery phase</td>
</tr>
<tr>
<td>55</td>
<td>4th test in recovery phase</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table II. Visual analogue lines (not to scale)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Alert ------------------------ Drowsy</td>
</tr>
<tr>
<td>(2) Mentally slow ---------------- Quick-witted</td>
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<tr>
<td>(3) Well co-ordinated ---------------- Clumsy</td>
</tr>
<tr>
<td>(4) Lethargic ---------------- Energetic</td>
</tr>
<tr>
<td>(5) Excited ------------------- Calm</td>
</tr>
<tr>
<td>(6) Tense ------------------ Relaxed</td>
</tr>
<tr>
<td>(7) Withdrawn ---------------- Sociable</td>
</tr>
<tr>
<td>(8) Depressed ---------------- Elated</td>
</tr>
</tbody>
</table>
signed randomly. Fifteen reaction times were summed and the average recorded.

**Tapping board** (fig. 1). Subjects were instructed to tap alternately two metal target areas 10 cm x 8.5 cm, set 50 cm apart, as many times as possible in 10 s. Three sessions with 10-s gaps between were performed. The apparatus automatically counted the number of taps over the 10-s session. The total number of taps over the three sessions was recorded.

**Mathematical problems.** The subject was instructed to complete as many random two-digit addition calculations as possible in 90 s. The number of sums attempted and the number correct were recorded.

Following each test session, subjects were asked which gas they thought they had received; whether the odour of the gas was pleasant, neutral or unpleasant; whether it was acceptable or not; and asked to record any side-effects noted during the inhalation. At a later date, subjects were asked if they experienced any after effects.

**Delivery apparatus**

A modified Boyle anaesthetic machine was used to deliver the inhalation agent(s), using standard oxygen and nitrous oxide rotameters and a Mark 3 isoflurane vaporizer. To allow delivery of 0.4% isoflurane, a separate oxygen rotometer was installed which bypassed the back-bar of the machine and allowed 10:1 dilution of the mixture passing through the vaporizer, this being set at 4%. Output concentrations were verified by an interference refractometer (Riken). Administration was via an airline pilot’s mask, which incorporated a small sampling tube at the expiratory valve, connected to a paramagnetic oxygen analyser (Servomex Ltd) with an attached pen recorder. Oxygen concentration was monitored throughout each session. During the assessment of the fit of the mask, 100% oxygen was given and the fit deemed acceptable if the measured oxygen concentration was greater than 95%. Full resuscitation equipment was available throughout the trial.

**Analysis**

Numerical data were compared using Freidman’s two-way analysis of variance. Pairs of data were then analysed using Wilcoxon Rank Sum test. Statistical significance was deemed to be achieved when \( P < 0.05 \).

### RESULTS

**Choice reaction time**

Both nitrous oxide and isoflurane decreased reaction time, the effect of isoflurane being greater than that of nitrous oxide (fig. 2). Unlike nitrous oxide, isoflurane did not reach its maximum effect until after 15 min. Within 5 min of stopping the administration, subjects regained values similar to those obtained while breathing oxygen.

**Tapping test**

An effect similar to that on reaction time was noted, both gases causing a decrease in the number of taps recorded (fig. 3). Again, recovery was noted within 5 min of discontinuation of the inhalation.

**Mathematical problems**

Both gases decreased significantly the number of sums attempted, isoflurane having a greater effect than nitrous oxide (fig. 4). After 15 min inhalation, the number of sums answered wrongly also increased significantly. No difference was noted once administration stopped.

**Visual analogue scales**

The effects of the inhalation of nitrous oxide or isoflurane were seen only in the scales rep-
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Fig. 2. Mean reaction time (± SEM) before, during and after inhalation of oxygen (●), nitrous oxide (■) and isoflurane (▲). *P < 0.05; **P < 0.01 = significant difference between nitrous oxide or isoflurane and oxygen; †P < 0.05; ‡P < 0.01 = significant difference between isoflurane and nitrous oxide. Some of the standard errors are omitted for clarity.

Fig. 3. Mean number of taps (± SEM) before, during and after inhalation of oxygen, nitrous oxide and isoflurane. (For explanation of symbols, see figure 2.)

representing physical and mental sedation (fig. 5). In contrast to objective testing, this effect continued for 15 min after stopping the inhalation. The effect of the inhalation on feelings of tranquillity was less marked, only isoflurane inducing a feeling of calmness after 5 min (fig. 6). Isoflurane increased feelings of depression compared with nitrous oxide or oxygen after 15 min inhalation. Subjects also felt more withdrawn 5 min after the discontinuation of isoflurane compared with nitrous oxide.

Other effects
The acceptability of the gas and its odour are described in table III. The odour of isoflurane was found significantly more unpleasant compared
FIG. 4. Mean number of sums attempted and mean percentage correct before, during and after inhalation of oxygen, nitrous oxide and isoflurane. (For explanation of symbols, see figure 2.)

FIG. 5. Mean visual analogue scores representing physical and mental sedation before, during and after breathing oxygen (●), nitrous oxide (■), and isoflurane (▲). **P < 0.01 = difference between anaesthetic gases and oxygen; *P < 0.05; †P < 0.01 = difference between isoflurane and nitrous oxide.
with that of nitrous oxide ($P < 0.05$, Chi-square test), although all but two of the subjects found the gas acceptable. Even with the perfumed spray, 10 of the 12 subjects correctly identified the gas mixture.

Seven subjects noted paraesthesia while breathing nitrous oxide, only one noting this while breathing isoflurane. Three subjects noted that background noise appeared magnified with nitrous oxide. Two subjects felt nauseated after breathing isoflurane, this continuing for some hours. One of these subjects vomited after the study. Another subject experienced slight nausea while breathing nitrous oxide.

**DISCUSSION**

The use of a variety of psychomotor tests for the assessment of sedative agents is well established [14]. It is important to choose a test that will give reliable results repeatedly so as to emphasize any differences between sedative agents. Hindmarch [15] and Scott, Whitwam and Wilkinson [16] discussed the effectiveness of a choice reaction timer although, unlike our study, they suggested an analysis of the component parts of the subject's
response—processing time (stimulus to start of movement) and movement time. Ghonheim, Mewaldt and Thatcher [17] first described the tapping test and, in conjunction with Kortilla and colleagues [18], found it sensitive both during and after the administration of nitrous oxide. However, in the present study, the effect was slight compared with isoflurane and did not persist into the recovery period.

None of the objective tests demonstrated any marked impairment of function once the administration of the gas had been discontinued. However, the subjective tests demonstrated impairment during the recovery period which was not detected by the objective tests. Subjective tests have been recommended for all such studies [15] and have been discussed at length previously [12, 19]. Clear differences were apparent between the groups expressing mental and physical sedation and those of tranquillity and mood. It may appear anomalous that a gaseous mixture intended for sedation and relief of anxiety did not induce any feelings of tranquillity in the volunteers. However, like Norris [12], who found little effect on the scoring of tranquillity, we are of the opinion that volunteers in familiar surroundings tend to be relaxed and calm initially, drugs making little difference.

Although the inspired concentrations were initially planned to be approximately equipotent in terms of calculated MAC values, the results demonstrated that an inhaled concentration of 0.4% isoflurane gave consistently greater effects than those from 25% nitrous oxide. It is possible that subjects hyperventilated more than anticipated during the trial, to give higher isoflurane alveolar concentrations than expected. Alternatively, the results may represent a real difference in potency at subanaesthetic concentrations. Using similar concentrations, Adams, Castro and Clarke [20] have already demonstrated differences in the amnesic effect of isoflurane, when compared with other anaesthetic agents.

The degree of sedation seen with 0.4% inspired isoflurane was greater than that which would be needed for most clinical procedures and the observers agreed that the volunteers would have fallen asleep had it not been for their will-power in concentrating upon the tests, and the occasional prompting of the supervising anaesthetist. Despite this degree of sedation, no unpleasant dreams or excitatory phenomena occurred and recovery was prompt, volunteers returning to normal during the afternoon of the study. As was foreseen by Philip [21], and reported by McLeod, Rammayya and Tunstall [9], the smell of the isoflurane was sometimes a problem. Although four volunteers found it pleasant, six found it unpleasant initially and in two of these, the smell persisted throughout the 20 min. One of these volunteers vomited after breathing the anaesthetic. In the case of nitrous oxide too, nausea was seen in one volunteer, even though the 25% concentration used rarely gives any problems in patients. Nausea and vomiting in volunteers may not indicate an equal risk to patients, as Parkhouse and colleagues [22] reported a high incidence of these effects in volunteers receiving nitrous oxide, although similar concentrations have been used in patients without serious problems. For these reasons, and because in practice lower inspired concentrations of isoflurane than 0.4% should suffice, we feel that the smell of isoflurane will not preclude its use in patients and that it will be worthy of clinical trial in patients in whom a period of intense sedation is needed with prompt return to a normal conscious state.

Assessment of the analgesic potency of isoflurane was omitted from these studies as it was felt that the measurement of pain would affect the psychological tests, although other workers have reported that subanaesthetic concentrations of isoflurane produce potent analgesia [9].

In transposing the results of our trial to dental sedation, allowance must be made for air dilution at the Dupaco mask which is commonly used. In dental techniques, 50% air dilution at the mask is common [23]; consequently, the delivered concentrations of an inhaled agent may need to be increased to compensate. In dental sedation techniques, as in others, the concentration of the inhaled agent is usually adjusted according to the patient’s response rather than using a fixed concentration as was used in this trial. A preliminary study has been completed and indicates that isoflurane would be of value for sedation in dentistry [24].

In conclusion, isoflurane was an acceptable alternative to nitrous oxide in most of the volunteers. For clinical use, less than 0.4% should be sufficient and a decrease in concentration towards the end of the clinical procedure may be necessary to avoid excess sedation and ensure a more rapid recovery. The problem of nausea and the specific analgesic effect of isoflurane require further study.
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REFERENCES