ARTERIAL CONCENTRATIONS OF NITROUS OXIDE DURING INTERMITTENT PATIENT-CONTROLLED INHALATION OF 50% NITROUS OXIDE IN OXYGEN (ENTONOX) DURING THE FIRST STAGE OF LABOUR

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SUMMARY

Measurements were made in 15 mothers of the arterial concentrations of nitrous oxide at the end of periods of inhalation of 50% nitrous oxide. The mean arterial concentrations, from all the patients, would be equivalent to breathing 26.4% nitrous oxide until equilibrium had been reached between the inspired concentration and the blood. The low measured blood levels are related to such factors as the short duration of inhalation, ventilation-perfusion defects in labour and the almost complete elimination of nitrous oxide between each contraction.

Theoretical studies of uptake and elimination of methoxyflurane during intermittent administration in labour made by Mapleson (1969) and by Waud and Waud (1970) predicted that a progressive rise in blood levels would occur if methoxyflurane was breathed intermittently but in an entirely regular manner during labour. However, this was not borne out either in clinical trials (Major, Rosen and Mushin, 1967; Jones et al., 1969) or by actual measurements of arterial concentration during labour (Latto, Rosen and Molloy, 1972). It was demonstrated that the mother usually breathes less methoxyflurane as labour progresses, so maintaining a reasonably steady blood level. In this way, the mother controls the uptake of methoxyflurane.

In the case of nitrous oxide, when this is used for analgesia, the timing of inhalation is very important. However, theoretical prediction was that after initial inhalation, a blood concentration would be present which should make the timing of subsequent inhalation less critical (Mapleson, 1969). In view of the difference between the theoretically predicted and experimental findings with methoxyflurane, it was important to determine what blood levels of nitrous oxide, when inhaled intermittently, occur in practice during labour.

METHOD

Permission.

Mothers were approached before labour commenced, and the purpose of the investigation was outlined. Written informed consent was obtained to insert an arterial cannula (Graham No. 19 Venflon).

Selection and instructions.

Patients who had received training in psychoprophylaxis were not included as it was intended to study a population as close as possible to that usually having inhalation drugs in labour. Nitrous oxide was administered either at the request of the patient, or when the midwife considered analgesia was required. Patients were instructed to breathe nitrous oxide as soon as they felt a contraction starting so as to obtain maximum pain relief. When the patient first felt the contraction she breathed from the face-piece and removed it when the pain had gone. No restriction was made on the use of other analgesics or sedative drugs by the midwife.

Measurements.

A 50% nitrous oxide and 50% oxygen mixture was breathed from an Entonox apparatus (BOC Ltd). The inspiratory flow was measured with a pneumotachograph (Fl Mercury Electronics), whose output was recorded. The pneumotachograph signal was integrated so as to derive tidal volume and cumulative volume. The integrator and recorder were calibrated each time before use with a 50% nitrous oxide and 50% oxygen mixture (Appendix).

The ulnar collateral circulation was assessed and if satisfactory the radial artery was cannulated just before Entonox was required. After emptying the cannula, approximately 2-ml samples of blood were taken for analysis of arterial concentrations of nitrous oxide. An event marker was used to record the time.

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of sampling on the recorder. Samples were taken over a period of about 5 seconds at the beginning and end of periods of inhalation of nitrous oxide. In a few patients, additional samples were taken 30 and 60 seconds after inhalation of nitrous oxide had ceased in order to study elimination. In 1 patient, additional samples were taken 15 seconds after the start of inhalation to study uptake. The blood levels were analysed within 24 hours by gas chromatography (Molloy, Latto and Rosen, 1973).

RESULTS

Measurements of arterial concentrations of nitrous oxide were made in 15 mothers (4 primigravidae and 11 multigravidae). Their mean age was 25.4 years (SD 5.9) (range 19–41). The mean of the total period during which nitrous oxide was inhaled intermittently was 46.4 min (SD 17.7) in the first stage of labour. The mean duration of each inhalation was 0.71 min (SD 0.19). Ventilatory measurements were made only in 13 mothers.

Typical case (fig. 1).

Measurements were made either at the end or the beginning of periods of inhalation of nitrous oxide (fig. 1). These concentrations were considered to represent the maximum and minimum blood levels of nitrous oxide respectively. Arterial concentrations are expressed both as mg/100 ml and the percentage concentration with which the blood would be in equilibrium. It can be seen that the samples measured at the end of periods of inhalation are approximately 65% of the level at equilibrium with an inspired concentration of 50% nitrous oxide (38.14 mg/100 ml). The samples measured at the beginning of periods of inhalation are approximately 10% of the equilibrium concentration with 50% nitrous oxide.

**The mean arterial nitrous oxide concentration.**

The mean of the concentrations at the beginning and the mean of those at the end of the periods of inhalation were calculated in each case (table I). The range of the mean arterial concentrations at the beginning of periods of inhalation is from 0.2 mg/100 ml to 6.2 mg/100 ml. The range of the mean arterial concentrations at the end of periods of inhalation is 8.5 mg/100 ml to 28.3 mg/100 ml.

The mean of the mean concentrations at the beginning of the periods of inhalation is 2.67 mg/100 ml. The mean of the mean concentrations at the end of periods of inhalation is 20.15 mg/100 ml.

The mean of the mean of the samples measured at the beginning of periods of inhalation as a percentage of the mean of the samples measured at the end of periods of inhalation is 12.5% (SD 7.36).

**Elimination of nitrous oxide.**

Arterial samples were taken immediately after inhalation of nitrous oxide ended and again 30 and 60 seconds later. The means of these measurements in 3 patients (a total of eleven contractions) are plotted in figure 2. It is clear that the fall in blood concentration is rapid and roughly exponential. The mean concentration had fallen to 8.2 mg/100 ml at the end of 30 seconds which is 35% of the initial concentration.

**Uptake of nitrous oxide.**

In 1 patient arterial samples were taken just before a period of inhalation of nitrous oxide, then 15 seconds after the start of the period of inhalation and at the end of the period of inhalation for six contractions. The means of the six samples taken at each time are plotted in figure 3. Approximately exponential changes in arterial concentration are demonstrated. At 15 seconds after the start of inhalation the mean blood concentration was 13.4 mg/100 ml which is 72% of the way from the initial to the final concentration.
### ARTERIAL CONCENTRATIONS OF NITROUS OXIDE

**Table I.** The mean concentrations of nitrous oxide at the beginning of periods of inhalation and at the end of periods of inhalation. The concentrations at the beginning are shown as a percentage of those at the end of periods of inhalation.

<table>
<thead>
<tr>
<th>No. in series</th>
<th>Mean duration of each inhalation (min)</th>
<th>Mean period of inhalation (min)</th>
<th>Mean (± 1 SD) of samples measured at beginning of periods of inhalation (mg/100 ml) (a)</th>
<th>No. of samples</th>
<th>Mean (± 1 SD) of samples measured at end of periods of inhalation (mg/100 ml) (b)</th>
<th>No. of samples</th>
<th>(a) as % of (b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.77</td>
<td>47</td>
<td>6.2 ± 0.6</td>
<td>5</td>
<td>23.7 ± 5.6</td>
<td>7</td>
<td>26.2</td>
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<td>2</td>
<td>0.62</td>
<td>14.5</td>
<td>1.9 ± 0.9</td>
<td>5</td>
<td>15.5 ± 5.3</td>
<td>6</td>
<td>12.2</td>
</tr>
<tr>
<td>3</td>
<td>—</td>
<td>30</td>
<td>2.7 ± 2.2</td>
<td>9</td>
<td>17.1 ± 5.8</td>
<td>9</td>
<td>15.8</td>
</tr>
<tr>
<td>4</td>
<td>—</td>
<td>25</td>
<td>1.4 ± 0.7</td>
<td>6</td>
<td>12.8 ± 2.6</td>
<td>7</td>
<td>10.9</td>
</tr>
<tr>
<td>5</td>
<td>0.67</td>
<td>73.7</td>
<td>4.3 ± 1.8</td>
<td>5</td>
<td>19.2 ± 5.1</td>
<td>14</td>
<td>22.4</td>
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<tr>
<td>6</td>
<td>0.87</td>
<td>51.2</td>
<td>0.4 ± 0.5</td>
<td>7</td>
<td>15.5 ± 3.1</td>
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<tr>
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<td>41.4</td>
<td>3.7 ± 1.6</td>
<td>6</td>
<td>21.8 ± 3.9</td>
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<td>49.8</td>
<td>0.5 ± 0.6</td>
<td>9</td>
<td>23.7 ± 4.5</td>
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<td>2.1</td>
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<td>9</td>
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<td>45.8</td>
<td>5.7 ± 3.1</td>
<td>10</td>
<td>28.3 ± 5.8</td>
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<tr>
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<td>11</td>
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<td>41.1</td>
<td>0.2 ± 0.4</td>
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<td>8.5 ± 4.4</td>
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<tr>
<td>12</td>
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<td>2.9 ± 0.5</td>
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<td>24.1 ± 6.7</td>
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<td>13</td>
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<td>2.9 ± 2.5</td>
<td>5</td>
<td>19.3 ± 7.6</td>
<td>5</td>
<td>15.0</td>
</tr>
</tbody>
</table>

**EXCRETION OF NITROUS OXIDE**

**Arterial concentration of Nitrous Oxide (mg/100ml)**

**UPTAKE OF NITROUS OXIDE**

**Arterial concentration of Nitrous Oxide (mg/100ml)**

**FIG. 2.** The fall in arterial concentration of nitrous oxide. Samples measured at the end of periods of inhalation and at 30 and 60 seconds after the period of inhalation of nitrous oxide. The mean and standard deviations of eleven measurements in 3 patients are shown.

**FIG. 3.** The arterial concentrations of nitrous oxide measured before inhalation of nitrous oxide, at 15 seconds after the start of inhalation and at the end of periods of inhalation of nitrous oxide. The mean and standard deviation of six measurements in 1 patient are shown.
Ventilation and uptake of nitrous oxide.

The increase in concentration of nitrous oxide from the beginning to the end of periods of inhalation could be compared with the mean ventilation during the corresponding uterine contraction. The mean volume of nitrous oxide inhaled for each of 97 contractions in 13 patients was 15.0 l. (SD 9.6) and the mean increase in arterial concentration of nitrous oxide was 19.2 mg/100 ml.

A regression of the difference between the nitrous oxide concentration in the samples taken at the beginning and the end of periods of inhalation on the volume ventilation reveals a highly significant correlation \( (P<0.0005) \) \( y = 14.39 + 0.32x \) \( (y=\text{concentration difference in mg/100 ml}; x=\text{volume ventilation in litres}) \). This substantiates the accuracy of both ventilation and blood-nitrous oxide measurements. The mean minute ventilation is therefore 20.8 l./min which is typical of well established labour (Davies et al., in preparation).

Analysis of trends in blood levels.

In order to examine the effects of the progress of labour on arterial blood levels for each patient, the samples at the ends of periods of inhalation were compared with the times since inhalation of nitrous oxide first started by regression analysis. The time the patient first started to inhale the nitrous oxide is designated zero time. In only two cases was there a significant linear increase in concentration \( (P<0.05) \).

In a further three cases a gradual rise in concentration was noted showing a significant positive quadratic trend \( (P<0.05) \). The other ten cases showed no statistically significant relationships.

**DISCUSSION**

The mean arterial blood concentration of nitrous oxide at the end of periods of inhalation was 20.1 mg per cent which is equivalent to breathing 26.4% nitrous oxide until equilibrium between the inspired concentrations and the blood is reached. In a previous study (Jones et al., 1969) it was shown that with continuous administration of nitrous oxide a mean concentration of 41.2% was required for optimum pain relief. This is 14.8% (41.2% minus 26.4%) more than the mean concentration of nitrous oxide in our patients. Furthermore, the nitrous oxide concentration used by Jones and his associates (1969) was limited to that which would not produce a marked reduction in the conscious level. It is plausible to suggest that an even higher concentration might have been tolerated briefly at the peak of the contraction had nitrous oxide not been given continuously. The pain of contractions stimulates awareness and therefore would reduce the likelihood of the patient becoming unconscious. In the period between a contraction when there is no pain stimulus a similar concentration of nitrous oxide might produce unconsciousness. If nitrous oxide is breathed intermittently, theoretically at least, better pain relief would be provided with higher blood levels of nitrous oxide at the peak of pain than the steady level required when it is administered continuously.

It is surprising that the mothers did not achieve higher blood concentrations. One reason must be the delayed approach of arterial to alveolar nitrous oxide which has been demonstrated in the dog and man (Eger et al., 1966). In that study, there was a 10–20% difference between arterial and alveolar levels after a half-minute of nitrous oxide ventilation decreasing to 5–10% by 4 minutes. Since the duration of inhalation of mothers in labour is about 30–60 seconds there is likely therefore to be a 10–20% difference between the alveolar and the arterial tensions.

Increased ventilation-perfusion abnormality probably exists during labour. Rorke, Davey and DuToit (1968) showed that during Caesarean section with an inspired oxygen concentration of 33.3 or 66.6% the mean maternal arterial oxygen tensions were 135 and 255 mm Hg respectively. These oxygen tensions are lower than theoretically predicted from a "perfect" lung. These findings were confirmed by Galbert and Gardner (1972) who studied 100 mothers undergoing Caesarean section with a 60 or 75% inspired oxygen concentration whose mean maternal arterial oxygen tensions were 184.5 and 283.7 mm Hg respectively. In mothers breathing 50% nitrous oxide and 50% oxygen for analgesia, similar abnormalities might occur. This would contribute to the discrepancy between the measured and the predicted arterial blood levels of nitrous oxide found in this study. However, an important factor in reaching a satisfactory blood level is the almost complete elimination of nitrous oxide by the beginning of the next inhalation (fig. 2). Each period of intermittent inhalation must then be a re-induction during which there is hardly time for the patient to achieve the optimum level of nitrous oxide analgesia.

The value of intermittent nitrous oxide analgesia in obstetrics could probably be improved substantially if a method of increasing the rate of uptake or of reducing the rate of fall in blood nitrous oxide level could be found. One approach would be to administer a higher fixed concentration of nitrous
oxide; uptake would then be more rapid. This method has been used in several clinical trials using from 60 to 80% nitrous oxide in oxygen (McAneny and Doughty, 1963; Baird et al., 1970). However, the results showed that some mothers became unconscious, probably because they hyperventilated during a contraction or went on breathing the nitrous oxide when the pain of contraction was over. The risk associated with these higher concentrations was therefore not considered to be worth the improvement in the pain relief. Clearly a method which depends on a rapid uptake could be expected to overshoot occasionally and therefore to cause unconsciousness.

In the more traditional approach, the inhalation of nitrous oxide is started before the uterine contraction begins. An attempt is made to do this by timing the period between contractions. In practice it is difficult for mothers and midwives to follow this plan probably because the midwife has to be in constant attendance if it is to work; in hospital it is rarely possible for the midwife to be there for every contraction. Furthermore, the success of the method depends upon the duration between contractions being fairly even which often they are not.

A modification of this technique suggests itself. Instead of timing the start of inhalation before the contraction begins, it might be equally effective if the mother took a few breaths of nitrous oxide in the period between contractions. It can be seen from figure 2 that the blood level has fallen substantially after 20–30 seconds. If the mother took a few breaths within that period and intermittently thereafter, until the next contraction started, the blood level of nitrous oxide would be raised at the start of the next contraction when she would inhale continuously until the pain was subsiding. This would reduce the time required to build up the blood concentration. In a pilot study this method appeared to work fairly well although such substantial encouragement was necessary to get the mother to collaborate that it is doubtful whether it will prove to be a practical proposition.

Alternatively, the mother could inhale nitrous oxide continuously in a concentration which would not result in any mother becoming unconscious. On the basis of a study carried out to provide sedation for conservative dentistry (Edmunds and Rosen, in preparation), an inhaled concentration of about 20–25% nitrous oxide might be suitable. This has been tried in a few obstetric patients, the mothers breathing nitrous oxide and oxygen through a nasal catheter. This provided a basal blood level of nitrous oxide and at each contraction the mother inhaled 50% nitrous oxide and 50% oxygen by a facepiece. This appears to be a promising means of enhancing the effectiveness of nitrous oxide.

An additional advantage of administering nitrous oxide and oxygen continuously would be that it becomes possible to deliver higher oxygen concentrations to the mother throughout labour. If this were considered undesirable then the nitrous oxide could be mixed with air and oxygen to give any inspired concentration of oxygen.

The point has been made that intermittent inhalation could be more effective than continuous administration because the blood concentration of nitrous oxide when pain is present could be higher than when there is no pain. To put this into practice the mother should be encouraged to remove the mask from her face as soon as the contraction starts to recede so that the blood level of nitrous oxide will then fall rapidly to avoid unconsciousness in the period between contractions.

The majority of mothers obtain reasonable pain relief with nitrous oxide as it is used at present; although only about 11% claim complete relief and 30% say they have little or no relief (Rosen et al., 1969). This investigation has shown what anaesthetists and obstetricians always suspected, namely that the inhalation of the nitrous oxide must be timed meticulously. However, because of the differences found in this study between inhaled and arterial blood levels, it does not seem likely even under the most favourable circumstances that optimum pain relief can be achieved without major improvements in the method of administration.

APPENDIX

Calibration procedure for recording ventilation.

(1) Stabilization. Thirty minutes was allowed for stabilization after switching on.

(2) Flow. The input to the micromanometer from the pneumotachograph was linear up to 300 l/min of air. For calibration 40, 30, 20 and 10 l/min of 50% nitrous oxide in oxygen were drawn through a calibrating flowmeter from the Entonox cylinder with the pneumotachograph connected in series. The scale reading was adjusted with a multi-turn potentiometer.

(3) Cumulative volume. 30 l/min was drawn through the pneumotachograph and a check made that the 30 l full-scale deflection of the cumulative volume took exactly 1 minute.

(4) Tidal volume. Tidal volumes of 1 l and 0.5 l were delivered to the pneumotachograph from a sine-wave flow generator calibrated with a Wright’s meter. The scale deflection was then adjusted accordingly. The outputs were taken to a Devices M4 recorder which was calibrated to give a convenient scale.
Intrauterine pressure. The intrauterine pressure tracing when available was calibrated by the obstetrician from 0–100 mm Hg. The height of the peaks were then marked on the recorder.

ACKNOWLEDGEMENTS

We would like to record our thanks to Professor W. W. Mushin, C.B.E., and Dr W. W. Mapleson, D.Sc. for their advice and encouragement.

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REFERENCES


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THE ANNUAL GENERAL MEETING AND SCIENTIFIC SYMPOSIUM
of the Faculty will be held on SATURDAY, MAY 18, 1974.