ANAESTHESIA FOR CAESAREAN SECTION

Analysis of Blood Concentrations of Methoxyflurane using 0.1 per cent Methoxyflurane and 40 per cent Oxygen

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SUMMARY

In fifteen mothers undergoing elective Caesarean section methoxyflurane 0.1 per cent vapour was added before the birth of the infant to a mixture of 40 per cent oxygen and 60 per cent nitrous oxide. Analysis of uptake and excretion of methoxyflurane was performed. Prompt recovery of consciousness occurred at the end of the procedure. In none of the mothers was there evidence of awareness during the procedure. There was no relationship between the Apgar score of the infants at one minute after delivery and the umbilical vein methoxyflurane concentration at delivery, and no evidence that methoxyflurane supplementation was responsible for foetal depression in this series.

Two different anaesthetic techniques for Caesarean section have recently been described (Moir, 1970; Crawford, 1971). In these halothane 0.5% and methoxyflurane 0.1% respectively were added to a nitrous oxide/oxygen mixture to prevent awareness. Methoxyflurane was, however, only used after delivery of the infant in order to avoid possible foetal depression by this agent. The evidence available, however, suggests that low concentrations of methoxyflurane do not cause foetal depression (Siker et al., 1968; Clark et al., 1970; Latto, Rosen and Molloy, 1972).

A detailed assessment of an alternative technique was therefore made, using a methoxyflurane 0.1% supplement from the time of induction and using a higher inspired oxygen concentration than that used by Crawford (1971).

METHOD

Patient selection and permission.

This series was confined to fifteen patients undergoing elective Caesarean section. Informed consent for radial artery cannulation was obtained from every patient.

Anaesthetic technique.

Patients were prepared as usual; they were starved for 6 hr, and 15 ml magnesium trisilicate was given orally ½ hour preoperatively. Atropine 0.6 mg was given intramuscularly 1 hour preoperatively or intravenously at induction.

All patients were pre-oxygenated for 2–3 min and anaesthesia was then induced with sodium thiopentone 250 mg, followed by suxamethonium 100 mg to facilitate intubation. Pressure was maintained on the cricoid cartilage to prevent regurgitation following loss of consciousness. After the affects of suxamethonium showed signs of wearing off, relaxation was maintained with pancuronium bromide 6.0 mg.

The patients were ventilated with nitrous oxide 7 l./min and oxygen 5 l./min (approximately 40%) using a Manley ventilator set to deliver a tidal volume of 700 ml. Methoxyflurane 0.1% was given from a previously chromatographically calibrated Pentec vaporizer. After delivery, the gas flow was changed to nitrous oxide 8 l./min and oxygen 4 l./min, with no change in the methoxyflurane concentration in order to decrease the possibility of awareness in the post-delivery phase. Methoxyflurane administration was discontinued when skin closure was almost complete and the effect of the relaxant was reversed with atropine 1.2 mg and neostigmine 2.5 mg. Ventilation continued with 100% oxygen at the end of the operation, and the endotracheal tube was removed only when the eyes opened in response to command.

The anaesthetic was administered by the anaesthetist on “maternity call”, and arterial cannulation and measurements were made by one of the authors.

Measurements and sampling.

Immediately after intubation, a 19 s.w.g. cannula
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(Venflon) was inserted into the radial artery by direct percutaneous puncture. If the first attempt failed for any reason, only one more attempt was made. The adequacy of the ulnar collateral circulation was assessed prior to cannulation.

The time from the injection of thiopentone to the start of methoxyflurane inhalation was noted. The latter was referred to as "zero time". After emptying the dead space of the cannula samples of approximately 2 ml were taken for analysis of methoxyflurane concentrations. The cannula was flushed with heparin saline 1 unit/ml between sampling. Samples were taken intermittently and also at certain other times, namely: (a) at delivery of the infant; (b) when methoxyflurane inhalation was discontinued; and (c) when the patient opened her eyes on command. A sample was also taken from the umbilical vein by the obstetrician immediately after delivery. Samples were analyzed by gas chromatography, using a silicone oil extraction technique (Jones, Molloy and Rosen, 1972).

Apgar scores of the infants were independently assessed by a paediatrician at 1 and 5 min after delivery. Mothers were asked about awareness and dreams at 1 hr and approximately 24 hr after delivery. At the latter time, the site of the arterial cannulation was examined for bruising and change in the pulse, and the patient was questioned about any symptoms referable to cannulation.

RESULTS

Analysis of arterial concentration was performed on 15 mothers. There were 2 primagravidae and 13 multigravidae. Their mean age was 31.2 yr (SD 5.1).

Arterial concentrations of methoxyflurane are shown in two patients weighing 98.6 and 47.7 kg respectively (figs. 1 and 2). A progressive rise in arterial concentration while inhaling methoxyflurane is shown. The rise was initially rapid and then became much slower. The maternal arterial concentration at delivery can be compared with the foetal umbilical vein concentration. There was a rapid fall in concentration after discontinuing methoxyflurane inhalation. The arterial concentration when methoxyflurane was discontinued (the maximum concentration) and the concentration when the patient opened her eyes on command are shown. Assuming a blood-gas partition coefficient of 13 (Eger and Shargel, 1963), the arterial concentration at equilibrium while inhaling methoxyflurane 0.1% was calculated to be 7.9 mg/100 ml. The maximum concentrations of 4.2 and 2.2 mg/100 ml respectively are approximately 53% and 28% of the equilibrium value of 7.9 mg/100 ml.

Umbilical vein and maternal arterial concentration at delivery.

These are shown in figure 3. The mean time between the start of methoxyflurane inhalation and delivery was 9.7 min (SD 2.9, range 4–15). The mean time between the injection of thiopentone and
Fig. 3. Maternal and foetal methoxyflurane concentrations (mg/100 ml) from 15 patients at delivery. ○ Maternal arterial concentration; ■ Umbilical vein concentration.

inhalation of methoxyflurane was 103 sec (SD 27).

The mean maternal arterial concentration at delivery and the mean umbilical vein concentration are shown in table I. In all cases the umbilical vein concentration was less than the corresponding maternal arterial concentration. The mean umbilical vein concentration was significantly less than the mean maternal concentration at delivery (P<0.001; t = 7.11). There is a significant relationship between the duration of inhalation of methoxyflurane and the foetal umbilical vein levels (P<0.05 for linear regression).

There is a significant regression of umbilical vein methoxyflurane concentration on time (P<0.01). There is neither a significant linear or quadratic relationship between maternal arterial concentration at delivery and time (P=0.1 and P=0.09). The quadratic regression is more nearly significant than the linear, as might be expected from observation of figs. 1 and 2.

**Apgar score and umbilical vein methoxyflurane concentration.**

The mean Apgar score at 1 min was 7.5 (SD 2.1, range 2–9) and the mean Apgar score at 5 min was 9.5 (SD 0.6, range 8–10). There was no correlation between Apgar scores at 1 min and the umbilical vein methoxyflurane concentration (P>0.3). All the Apgar scores were 9 or 10 at 5 min except in case No. 4. Case No. 4 had an Apgar score of 2 at 1 min, and 8 at 5 min. The mother had pre-eclamptic toxaemia and the infant inhaled some liquor during delivery. The infant was intubated and liquor aspirated from the trachea.

**Regression analysis of both these concentrations and time showed a highly significant trend (P<0.0005). This straight line intercepts the y axis at 1.374 (y = 1.374 + 0.03619x). This indicates that the build-up in concentration becomes slower after the initial rapid uptake phase.**

**Maximum maternal arterial concentrations.**

These, together with the level at delivery, are shown in figure 4. The mean of the maximum concentration is 2.78 mg/100 ml (SD 0.77). Regression analysis of the maximum concentration on time showed a non-significant correlation (P>0.25). The mean time of inhalation of methoxyflurane is 38.5 min (SD 7.9).

**Fall in arterial concentrations.**

The fall in arterial concentration from the maximum level to a level at which the patient opened her eyes on command is shown in figure 5. The mean concentration at which the patient opened her eyes was 1.19 mg/100 ml (SD 0.38). The mean time between switching the vaporizer off and opening eyes to command was 6.2 min (SD 2.1). This recovery phase represents excretion of both nitrous oxide and methoxyflurane.

The mean level at which the patient's eyes open to command is 42.9% of the mean maximum level. Both levels are, however, well below the minimum alveolar concentration for anaesthesia (MAC) which is 0.16 vols% for methoxyflurane (Saidman et al.,

**Table I. Mean maternal arterial concentrations of methoxyflurane from 15 patients at delivery, when the vaporizer was turned off and when the eyes opened on command. The mean umbilical vein methoxyflurane concentration is also shown.**

<table>
<thead>
<tr>
<th>Sample time</th>
<th>Methoxyflurane concentration (mg/100 ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal</td>
<td></td>
</tr>
<tr>
<td>At delivery</td>
<td>1.72 ± 0.53</td>
</tr>
<tr>
<td>Vaporizer turned off</td>
<td>2.78 ± 0.77</td>
</tr>
<tr>
<td>Eyes open on command</td>
<td>1.19 ± 0.38</td>
</tr>
<tr>
<td>Foetal</td>
<td></td>
</tr>
<tr>
<td>Umbilical vein concentration at delivery</td>
<td>0.54 ± 0.36</td>
</tr>
</tbody>
</table>
1967), or an arterial concentration of 13.5 mg/100 ml assuming a blood-gas partition coefficient of 13 (Eger and Shargel, 1963).

Awareness and dreams.

In no case was there any evidence of awareness. Two cases reported having dreams, neither of them unpleasant. However, 3 patients were noted to be sweating during the procedure.

DISCUSSION

Crawford (1962), Hartridge and Wilson (1963), and Wilson and Turner (1969), reported an incidence of awareness of approximately 2% in patients undergoing Caesarean section with an unsupplemented nitrous oxide and oxygen anaesthetic. In an attempt to eliminate this incidence of awareness Moir (1970) described a technique in which 0.5% halothane was used to supplement a 50% nitrous oxide 50% oxygen mixture which was delivered at a minute volume of 8 l./min; the incidence of awareness was reduced to zero. There was no depression of Apgar scores at birth or increased bleeding.

Crawford (1971) described a technique in which hyoscine 0.6 mg was injected intravenously before induction with thiopentone; anaesthesia was initially maintained with a mixture of oxygen 33.3% nitrous oxide 66.6%, using a ventilatory minute volume of 12 l./min. Methoxyflurane 0.1% was added to the inspired mixture after the birth of the baby. There was no report of awareness with use of this technique. The possibility of causing foetal depression by administration of methoxyflurane was thus avoided. Crawford stated that awareness occurs most commonly in the pre-delivery phase, or possibly more frequently at delivery in Caesarean sections. The absence of awareness in this unsupplemented pre-delivery phase was explained partly on the basis of retrograde amnesia induced by methoxyflurane given after delivery. Crawford, et al. (1969) also consider that hyoscine is a powerful anterograde amnesic agent. Thus it is likely to be the combination of these two factors that is effective in preventing awareness, particularly in those patients in whom there is a long induction-delivery interval. There is, however, a delay of 20-30 min before significant anterograde amnesic effects appear after intravenous hyoscine (Pandit, 1970). It would, therefore, appear that awareness would be more effectively prevented if hyoscine were to be administered preoperatively rather than at induction. It is considered likely, in view of the rapid initial uptake of methoxyflurane, that this form of supplementation is as likely to prevent memory or awareness in the period between induction and delivery as is the anterograde amnesia induced by hyoscine.

Avoidance of methoxyflurane before delivery is, however, not universally recommended and indeed Le G. Waldron (1971) introduces 0.2–0.5%
methoxyflurane at the time of pre-oxygenation which lasts 4–5 min. This is followed by a mixture of 50% oxygen in nitrous oxide with the same volatile supplement for maintenance. He states that patients anaesthetized with this technique are unaware, and that there is a reduction both in the induction dose of methohexitone and the dose of tubocurarine required for paralysis. The minute volume used is not recorded. He considers that the benefit of a higher inspired oxygen concentration on the foetus and the decreased risk of awareness for the mother outweighs the possible harmful effect of the volatile supplement on the foetus.

The anaesthetic technique for Caesarean section, in addition to abolishing the risk of awareness, should produce optimum foetal oxygenation and Apgar scores. Rorke, Davey and DuToit (1968) showed that Apgar scores in infants whose mothers were given an inspired oxygen concentration of 66% were higher than in those whose mothers were given an inspired oxygen concentration of 33%. They also showed that the optimum maternal arterial tension is approximately 300 mm Hg, above which level an increase in maternal $P_{A_{O_2}}$ caused a slight decrease in foetal umbilical vein $P_{O_2}$. A significant correlation was shown between Apgar scores at birth and umbilical vein and artery oxygen tensions. Baraka (1970) showed, however, that maximum umbilical vein oxygen tensions occurred with slightly lower maternal oxygen arterial tensions of 200–300 mm Hg. No measurements of blood-gas tensions were made in this series but improved Apgar scores might be expected to result from the higher inspired concentration of oxygen given before delivery.

Ivankovic, Elam and Huffman (1970) studied the effect of maternal hypercarbia on the clinical condition of the foetus. Higher one minute Apgar scores were observed in infants from a hypercarbic group of patients than in a normocarbic control group. It was postulated that carbon dioxide was responsible for the rapid initiation of respiration in the neonate. Mothers ventilated at a respiratory minute volume of 12 l./min will have lower arterial tensions of carbon dioxide than mothers ventilated at a minute volume of 8 l./min. It is thus to be expected that initiation of respiration in the neonate would be more rapid in the latter group.

Clark and colleagues (1970) demonstrated a correlation between Apgar scores and both umbilical vein and artery methoxyflurane concentrations. However, they also showed that there was little effect on the foetus if low inspired concentrations of methoxyflurane were administered to the mother or if the duration for which a higher concentration was administered was kept short. Siker and associates (1968), however, found that no correlation could be established between foetal methoxyflurane levels and the condition of the infant at birth.

Higher umbilical vein concentrations of methoxyflurane were found in patients breathing methoxyflurane 0.35% for analgesia in labour (mean 1.25 mg/100 ml) than in the patients in this series (mean 0.54 mg/100 ml), and there was no evidence of foetal depression (Latto, Molloy and Rosen, 1972). Evidence of foetal depression was not found in a large field trial (Rosen et al., 1969). This evidence suggests that the umbilical vein methoxyflurane levels in the present study are unlikely to cause foetal depression. Measurements in this series have only been made in patients in whom the induction-delivery interval was short. The umbilical vein concentration would have been significantly higher had the induction-delivery interval been prolonged.

Wilson (1971) advocated the use of a methoxyflurane 0.1% supplement to a nitrous oxide 50% and oxygen 50% mixture before delivery. After delivery a low concentration of halothane was substituted for methoxyflurane, thus combining the recommendations of Crawford (1971) and Moir (1970). Halothane was substituted for methoxyflurane on the grounds that on account of the different pharmacokinetics of these two agents a faster maternal recovery would result with halothane. This sequence also prevents the possibility of halothane causing uterine relaxation and poor response to oxytocins. However, the mean time interval between switching off the vaporizer and opening of the eyes in this series was only 6.2 min. The maternal arterial concentrations at no time rose to anaesthetic levels and are comparable with analgesic levels that do not cause loss of consciousness. This technique also avoids the necessity of using two vaporizers and of exposing the mother to two different anaesthetic agents.

Any drug used at Caesarean section should be free from harmful effects to the mother. There have been reports of nephrotoxicity following methoxyflurane anaesthesia (Crandell, Pappas and MacDonald, 1966; Mazze, Shue and Jackson, 1971), but this appears to be a dose-dependent toxicity (Mazze, Trudell and Cousins, 1971). Maternal blood levels in this series were similar to those measured during intermittent inhalation of methoxyflurane 0.35%
for analgesia in labour (Latto, Rosen and Molloy, 1972). The mean volume of methoxyflurane 0.35% and air mixtures inhaled to provide analgesia in 15 mothers during labour was 286 l. (SD 194.4). (This volume is equivalent to 1001 l. of 0.1% methoxyflurane). The mean volume of methoxyflurane 0.1% inhaled in this series was 462 l. (SD 94.5). Thus, the mothers who were given methoxyflurane for analgesia received approximately twice as much as the mothers in the present series. No evidence of nephrotoxicity was observed in a series of mothers given methoxyflurane analgesia during labour (Rosen, Latto and Asscher, 1972), and it may be inferred that nephrotoxicity is unlikely to occur under these circumstances.

This method has been tested on only 15 mothers, thus no claim can be made about its efficiency in preventing awareness in large numbers of patients. Further work is clearly necessary to establish this. This method may be modified in a number of different ways. Hyoscine may be used as a premedicant. A higher oxygen concentration may be utilized in the pre-delivery phase since a 40% inspired concentration is lower than that necessary to achieve maximum Apgar scores. Higher concentrations of methoxyflurane may be used particularly if the patient appears to be lightly anaesthetized. A lower minute volume may be used and the possibility of adding a carbon dioxide supplement to maintain the end expired carbon dioxide tension at a fixed level may be considered. After the delivery of the infant there is little excuse for awareness and changes in technique, particularly in the inspired oxygen concentration, may be instituted immediately after delivery. Patients undergoing emergency Caesarean section who have received pethidine and who are tired may need less anaesthetic than patients undergoing elective Caesarean sections.

Important objectives of an anaesthetic for Caesarean section are the prevention of foetal depression and at the same time the prevention of maternal awareness. These two aims may be partially antagonistic. Thus provision of a high inspired oxygen concentration and, consequently, a low nitrous oxide concentration, is more likely to result in high Apgar scores, but may also result in an increased incidence of awareness. The addition of an adequate supplement to the basic nitrous oxide, oxygen anaesthetic prevents awareness but a high concentration of the supplement will cause lower Apgar scores. Lastly, pulmonary hyperventilation with nitrous oxide and oxygen mixtures helps to prevent awareness, but the resulting low maternal carbon dioxide tensions may well lead to lower Apgar scores in the infants.

The inspired oxygen concentration, the concentration of the supplement and the minute volume can be varied independently. The recommended settings of these three variables are at present arbitrarily fixed, and there does not appear to be sufficient evidence to define the optimum relationship between them.

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REFERENCES


L’ANESTHESIE DE LA CESARIENNE: ANALYSE DES CONCENTRATIONS SANGUINES DE METHOXYFLURANE, UTILISANT 0,1 POURCENT DE METHOXYFLURANE ET 40 POURCENT D’OXYGENE

SOMMAIRE
Chez quinze mères, subissant une césarienne élective, du méthoxyflurane à 0,1 pourcent a été ajouté avant la naissance de l’enfant, à un mélange de 40 pourcent d’oxygène et 60 pourcent de protoxyde d’azote. On a procédé à l’analyse de l’absorption et excrétion de méthoxyflurane. Rapide regain de la conscience a été noté à la fin de l’intervention. Aucune des femmes n’était consciente durant l’opération. Il n’y avait pas de relation entre le score Apgar des enfants après 1 minute et la concentration de méthoxyflurane dans la veine ombilicale, et aucune preuve dans cette série que l’addition de méthoxyflurane serait responsable d’une dépression fétale.

NARKOSE BEI DER SECTIO CAESAREA: METHOXYFLURANKONZENTRATIONSBESTIMMUNGEN IM BLUT NACH GABE VON 0,1% METHOXYFLURAN UND 40% SAUERSTOFF
ZUSAMMENFASSUNG

ANESTESIA PARA LA SECCION CESAREA: ANALISIS DE LAS CONCENTRACIONES SANGUINEAS DE METOXIFLURANO UTILIZANDO METOXIFLURANO AL 0,1 POR CIENTO Y OXIGENO AL 40 POR CIENTO

RESUMEN
En quince madres sometidas a seccion cesarea electiva fue añadido metoxiflurano al 0,1 por ciento en forma de vapor a una mezcla de oxigeno al 40 por ciento y oxido nitroso al 60 por ciento. Fue analizada la retencion y excrecion del metoxiflurano. Al final de este procedimiento hubo una rapida recuperacion de la consciencia. No hubo signos de consciencia en ninguna de las madres durante esta anestesia. No hubo ninguna relacion entre el grado Apgar de los infantes un minuto despues del parto y la concentracion de metoxiflurano en la vena umbilical ni prueba de que la adicion de metoxiflurano produjera depresion fetal en esta serie.