PLACENTAL TRANSFER OF METHOXYFLURANE

BY

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SUMMARY

Estimations of methoxyflurane levels in maternal arterial and umbilical cord, venous and arterial blood were made in forty-three patients. As was anticipated from the physical characteristics of the agent, transference across the placenta was early and relatively unrestricted. Apgar scoring of the infants was carried out and showed a low incidence of foetal depression. No correlation could be established between the state of the infant and umbilical vein methoxyflurane content. Patient reaction was very favourable, especially when compared with previous experience with ether. These findings suggest that methoxyflurane may be used to advantage during obstetric delivery and that adverse effects on the foetus may be avoided by the careful use of light planes of anaesthesia.

The extent to which an anaesthetic agent may be of value in obstetric practice depends on many factors. Of prime importance is its effect on the foetus and this in turn may be influenced by the rate at which it traverses the placental barrier. Although many mechanisms probably take part in placental transfer, inhalational anaesthetic agents pass mainly by simple diffusion (Moya and Thorndike, 1962).

The rate at which a drug diffuses across the placenta depends upon the difference in the maternal and foetal concentrations of the drug, and on the thickness and total surface area of the placenta. In addition diffusion is influenced by factors inherent in the drug itself such as molecular weight and spatial configuration, fat solubility and the extent to which it is ionized.

Brodie and his associates (Mayer, Maickel and Brodie, 1959; Brodie, Kurz and Schanker, 1960) studied the influence of both lipid solubility and degree of ionization of drugs on transference across the blood-brain barrier. They reported that substances readily traverse this barrier in their undissociated or non-ionized form, whereas dissociated or ionized compounds penetrate with difficulty. In addition, drugs with high fat solubilities traverse the barrier rapidly, whereas fat insoluble drugs penetrate poorly irrespective of their degree of ionization. Moya and Kvisselgaard (1961) stressed the striking similarity between the blood-brain barrier and the blood-placental barrier, and suggested that the same mechanisms obtain concerning placental transfer.

Although data are available concerning the placental transfer of ether (Smith and Barker, 1942; Cole and Kimball, 1943), cyclopropane (Apgar et al., 1957), nitrous oxide (Smith, 1940; Cohen et al., 1953) and halothane (Sheridan and Robson, 1959) the present authors have been unable to find any reference to the passage of methoxyflurane across the placenta in human investigations. Methoxyflurane has a low degree of dissociation and is highly lipid soluble (Eger and Shargel, 1963), factors which should favour rapid transfer across the placenta. However, in a number of clinical series (Boisvert and Hudon, 1962; Romagnoli and Korman, 1962) and in over 2,000 vaginal deliveries anaesthetized with methoxyfluorane by the present authors and their colleagues, foetal depression has not been a feature.

The present study, therefore, was undertaken to obtain data concerning the transference of methoxyflurane across the placenta and if possible to correlate this data with the clinical state of the newborn. In addition it was hoped that by measuring the levels of methoxyflurane in both venous and arterial cord blood some information might be obtained concerning foetal uptake of the agent.
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METHOD AND MATERIAL

A series of forty-three healthy, full-term parturient women, both primipara and multipara, having vaginal deliveries were studied. Drugs used for sedation and analgesia during the first stage of labour consisted principally of pentobarbitone and a combination of pethidine and hyoscine. Anaesthesia was induced with methoxyflurane, nitrous oxide and oxygen via a circle absorption system. Methoxyflurane was vaporized in a Pentec vaporizer outside the breathing circuit using 3 l/min each of nitrous oxide and oxygen. The initial dial setting on the Pentec was 0.5 per cent. This was gradually increased as necessary to between 1.0 and 1.5 per cent. At the moment the baby was delivered, a sample of maternal blood was drawn from a brachial or radial artery. The umbilical cord was clamped and cut in the customary fashion and a second clamp was then placed as close to the placenta as possible. After the delivery of the placenta the umbilical vein and arteries between the two clamps were separately cannulated and samples drawn. Methoxyflurane levels were measured by gas chromatography following extraction by carbon disulphide (Wolfson, Ciccarelli and Sikir, 1966). The mothers and newborns were divided into three groups depending on the number of minutes of methoxyflurane administration prior to clamping the umbilical cord: 0–10 minutes (Group 1); 10–15 minutes (Group 2); 15–25 minutes (Group 3). One minute after delivery the baby was scored according to Apgar's criteria (Apgar, 1953). The occurrence of minor movement, phonation and/or stridor was also recorded. On the day following delivery, the patient's subjective reactions to the experience were obtained by interview.

RESULTS

The average methoxyflurane concentrations of maternal arterial and umbilical arterial and venous blood are shown in table I. Technical difficulties made it impossible to obtain cord arterial samples in every case. Significantly higher concentrations of methoxyflurane in maternal arterial (t=2.0*), umbilical venous (t=2.8), and umbilical arterial (t=2.5) blood were seen in Group 2 when compared with Group 1. Significantly lower concentrations of methoxyflurane in maternal arterial (t=2.0) and umbilical venous (t=2.7) blood were seen in Group 3 when compared with Group 2. No difference was seen in umbilical arterial content between Groups 2 and 3. The differences in methoxyflurane content between Groups 1 and 3 were statistically significant only for umbilical artery specimens, Group 3 having a higher level (t=2.2). The differences between umbilical arterial and venous methoxyflurane content were significant in all groups. The magnitude of this difference, however, was considerably less in Group 3 than in either of the other two groups.

The earliest evidence of placental transfer of methoxyflurane in this study was observed in a patient delivered 2 minutes after the induction of anaesthesia. The concentration of methoxyflurane in the umbilical vein was 1.30 mg/100 ml, 65 per cent of the concentration in the maternal artery (2.0 mg/100 ml). The highest maternal blood level of methoxyflurane in this study was 12.0 mg/100 ml. This was seen in a patient in Group 1 (6 minutes of anaesthesia) and was associated with a cord venous level of 5.2 mg/100 ml and an Apgar score of 9 in the newborn. The highest cord venous level was 6.7 mg/100 ml. This was seen in a patient in Group 3 (16 minutes of anaesthesia) and was associated with a maternal level of 11.8 mg/100 ml and an Apgar score of 9 in the newborn.

<table>
<thead>
<tr>
<th>Group</th>
<th>Maternal arterial</th>
<th>Umbilical arterial</th>
<th>Umbilical venous</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6.78 ± 3.78</td>
<td>3.25 ± 1.14</td>
<td>0.92 ± 0.62</td>
</tr>
<tr>
<td></td>
<td>12 patients</td>
<td>48%*</td>
<td>(8 estimations)</td>
</tr>
<tr>
<td>Group 1</td>
<td>9.28 ± 3.79</td>
<td>6.57 ± 2.66</td>
<td>1.84 ± 1.16</td>
</tr>
<tr>
<td></td>
<td>14 patients</td>
<td>71%*</td>
<td>(11 estimations)</td>
</tr>
<tr>
<td>Group 3</td>
<td>7.40 ± 1.90</td>
<td>4.43 ± 1.52</td>
<td>1.84 ± 1.23</td>
</tr>
<tr>
<td></td>
<td>17 patients</td>
<td>60%*</td>
<td>(13 estimations)</td>
</tr>
</tbody>
</table>

*Student's t test.

*Per cent of maternal arterial concentration.
Of the forty-three babies in this series, six had Apgar scores of 6 or below (table II). In Group 1, two babies with scores of 6 and 3 had umbilical venous methoxyflurane levels of 4.6 and 2.0 mg/100 ml respectively. There was no apparent cause for the low score in the former, but in the latter the mother had received pethidine 150 mg within 2 hours of delivery. One baby in Group 2 with an umbilical venous methoxyflurane level of 3.3 mg/100 ml had an Apgar score of 4. This baby was born to an obese primiparous patient after a prolonged period of labour. In Group 3, three babies with scores of 6, 6, and 4 had umbilical venous methoxyflurane levels of 5.0, 3.5, and 2.0 mg/100 ml respectively. There was no apparent cause for this score in the former; the mother was born within 80 minutes her pethidine 100 mg had been given to the mother; the third was a difficult breech delivery.

The overall incidence of minor movement during anaesthesia was 34 per cent; 25 per cent phoned and 25 per cent exhibited stridor during delivery of the head. Neither nausea nor vomiting was seen in this group of mothers during the 24 hours following delivery.

Forty of the forty-three mothers in this group were interviewed on the day following delivery. Of these, fifteen had no memory of the event. The remaining twenty-five mothers expressed satisfaction with their experience. A number spontaneously mentioned that the odour was not objectionable, especially when compared to their prior experience with “ether” (nitrous oxide, oxygen, ether anaesthesia).

**DISCUSSION**

Human studies with ether (Smith and Barker, 1942), cyclopropane (Apgar et al., 1957) and halothane (Sheridan and Robson, 1959) have demonstrated rapid transfer of these agents across the placenta. The amount of agent transferred varies greatly with duration of anaesthesia and from patient to patient. Animal studies have revealed similar findings with trichloroethylene (Helliwell and Hutton, 1949, 1950). A relationship between the degree of foetal depression and the blood level of the agent was seen with ether (Smith and Barker, 1942; Cole and Kimball, 1943) but not with cyclopropane (Apgar et al., 1957). The average level of nitrous oxide after an unspecified length of anaesthesia was reported as 50 per cent of maternal venous concentration in one study (Smith, 1940) and as 58 per cent after 10-19 minutes of anaesthesia in another (Cohen et al., 1953).

**Table II**

Low Apgar scores in six newborn babies. Possible factors.

<table>
<thead>
<tr>
<th>Case</th>
<th>Group</th>
<th>Apgar score</th>
<th>Methoxyflurane concentration in maternal arterial blood (mg/100 ml)</th>
<th>Methoxyflurane concentration in cord venous blood (mg/100 ml)</th>
<th>Concentration of methoxyflurane in maternal arterial blood (as percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>3</td>
<td>4.00</td>
<td>2.00</td>
<td>50</td>
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<tr>
<td>2</td>
<td>1</td>
<td>6</td>
<td>5.70</td>
<td>4.60</td>
<td>80</td>
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<tr>
<td>3</td>
<td>2</td>
<td>4</td>
<td>11.30</td>
<td>3.30</td>
<td>29</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>6</td>
<td>7.60</td>
<td>5.00</td>
<td>71</td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td>6</td>
<td>6.50</td>
<td>3.50</td>
<td>53</td>
</tr>
<tr>
<td>6</td>
<td>3</td>
<td>4</td>
<td>6.50</td>
<td>2.00</td>
<td>31</td>
</tr>
</tbody>
</table>

Possible cause of foetal depression:

- Pethidine 150 mg within 2 hours of delivery
- Prolonged delivery in obese primiparous patient
- Pethidine 100 mg 80 minutes before delivery
- Difficult breech delivery
The present study indicated that methoxyflurane crossed the placental barrier early and in significant amounts. The average ratio of cord venous to maternal arterial methoxyflurane content increased from 48 per cent to 71 per cent from Group 1 to Group 2. This was probably due to the higher average concentration of methoxyflurane presented to the placenta in the latter group. The large standard deviations reflect the marked variations seen from patient to patient within each group.

As the duration of anaesthesia increased, the delivered concentration of methoxyflurane was usually reduced as an adequate plane of light anaesthesia was attained. This reduction was mirrored by the fall in maternal arterial and umbilical venous methoxyflurane concentrations from Group 2 to Group 3. The large umbilical cord arterio-venous difference in methoxyflurane content suggested that considerable foetal uptake of methoxyflurane occurred. This was not surprising in view of the reported solubility of methoxyflurane in adipose tissue, muscle and brain (Eger and Shargel, 1963). The reduction in arterio-venous methoxyflurane difference from Group 2 to Group 3 suggested that the rate of uptake by the foetus had diminished by the time period between 15 and 25 minutes after induction of anaesthesia. However, our inability to measure placental perfusion and umbilical arterial and venous flow made it impossible to derive any precise measurements of total foetal uptake of methoxyflurane in this study.

The Apgar scores of the infants in this series were impressively high. Six infants had scores of 6 or less (table II) and it is possible to speculate concerning aetiology in these cases. In case 1, although the percentage transference of methoxyflurane was average for the group, both maternal and cord venous levels were lower than average. These findings suggest reduced maternal uptake of methoxyflurane due to respiratory depression following pethidine. In cases 2 and 4 cord venous levels and percentage transference were both higher than average for their group but it should be noted that these levels were lower than the average cord venous levels in Group 2 which were unattended by foetal depression. In cases 3 and 6 a very low transference of methoxyflurane despite a high or average maternal level, in the face of prolonged or difficult delivery, suggests the possibility of impaired placental perfusion. In case 5 the findings were somewhat similar to those of case 1 but with smaller deviations from the average. In this case the mother had received a smaller dose of pethidine than did case 1 and the Apgar score was higher. In view of these results it seems reasonable to suggest that, in this series, methoxyflurane was not a major factor in the production of neonatal depression.

In general no correlation could be established between foetal methoxyflurane levels and condition of the infant at birth. These findings were similar to those previously mentioned with cyclopropane (Apgar et al., 1957) but unlike those with ether (Smith and Barker, 1942; Cole and Kimball, 1943). It must be pointed out, however, that the figures demonstrate early and relatively unrestricted transference of the drug across the placenta and suggest marked foetal uptake. The maternal blood levels of methoxyflurane were in most instances well below the average levels (11.1 mg/100 ml) associated with the earliest electroencephalographic changes during nitrous oxide, oxygen, methoxyflurane anaesthesia (Wolfson et al., 1967). Light anaesthesia was further attested to by the relatively high incidence of minor movement, phonation and stridor at various stages during the delivery. These findings suggest that the safety of methoxyflurane seen in this study was attributable to the light planes of anaesthesia produced.

REFERENCES


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TRANSFERT PLACENTAIRE UBERTRAGUNG VON METHOXYFLURAN

ZUSAMMENFASSUNG