EFFECTS OF METHOXYFLURANE (PENTHRANE) ANAESTHESIA IN CHILDREN* 

BY

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SUMMARY

Some circulatory and respiratory effects of methoxyflurane anaesthesia were studied in ten normal children. Arterial pressure was little altered by this anaesthetic and the changes observed resembled those produced by halothane rather than di-ethyl ether. The degree of respiratory depression during methoxyflurane anaesthesia was intensified by increasing the concentration of the inhaled vapour. There was no tendency to hyperglycaemia, either prior to or during surgery. Ventricular irregularities were not a feature of methoxyflurane anaesthesia, at either normal or elevated end tidal Pco₂ levels.

A previous study by Black and Love (1961) revealed that in children arterial pressure was elevated by di-ethyl ether and little altered by halothane. It was felt that it would be of interest to examine the effect of methoxyflurane on blood pressure under comparable conditions of study. A short investigation was therefore undertaken in order to evaluate some aspects of the cardiovascular response of children to this agent under controlled conditions. Studies made in dogs by Dobkin and Fedoruk (1961) and by Bagwell and Woods (1962) indicate that, as is the case with halothane, arterial pressure and ventricular contractile force are reduced by methoxyflurane in proportion to the concentration of the inspired vapour. Bamforth and her colleagues (1961) have shown that methoxyflurane sensitizes the heart to adrenaline in dogs, and on this account cardiac rhythm was studied at normal and elevated levels of end-tidal Pco₂ in some of the children. The response of the cardiovascular system to an anaesthetic agent depends largely upon the degree of sympathetic-adrenal activity which it produces, and this in turn may be reflected by changes in blood sugar concentration. Although Wasmuth and his associates (1960) reported that methoxyflurane anaesthesia caused hyperglycaemia in man, Millar and Morris (1961) found that blood sugar levels were within normal limits in the dog when this agent was inhaled. This discrepancy could be explained by species variation and it was therefore decided to investigate blood sugar changes in the children being studied.

METHODS

The ten subjects were children aged 5 to 11 years who were about to undergo minor surgery. The sole pre-anaesthetic medication was 0.65 mg atropine given subcutaneously 30 minutes before the study started. Anaesthesia was induced with 2.5 per cent thiopentone (4 mg/kg) and maintained with 75 per cent nitrous oxide and 25 per cent oxygen, using a facepiece with a non-rebreathing system incorporating a Ruben valve. After a 15- to 20-minute control period methoxyflurane was added to the inspired mixture using a Pentec vaporizer calibrated in the range 0.5 to 1.5 per cent v/v. Arterial pressure was estimated by the auscultatory method, and mean arterial pressure was calculated as diastolic pressure plus one-third of the pulse pressure. Cardiac rhythm was monitored using lead II electrocardiography and end-tidal Pco₂ was estimated by the rebreathing method of Campbell (1960).

Blood sugar concentrations were estimated in these ten children during methoxyflurane anaesthesia both prior to and during surgery, using the method described by Asatoor and King (1954). Varying degrees of hypercarbia were produced in four additional children by adding exogenous...
carbon dioxide to the mixture of inspired gases. The Pco₂ was elevated until either ventricular extrasystoles occurred or a level of approximately 90 mm Hg was attained. This procedure was carried out in two of the children during 1 per cent methoxyflurane anaesthesia followed by 1 per cent halothane anaesthesia, after a 15-minute interval. In the other two children the order was reversed, halothane being administered prior to methoxyflurane.

All the data reported in this investigation are based on observations made over a period of 20 to 30 minutes stable anaesthesia and before the commencement of surgery. Respiration was spontaneous and unassisted at all times during the studies.

Standard statistical methods were used to determine the significance of differences between observations, a difference being considered significant when the P value was less than 0.05.

RESULTS

The effects of the inhalation of clinical concentrations of methoxyflurane on heart rate, mean arterial pressure and end-tidal Pco₂ on the ten children studied are displayed in table I.

Circulatory changes.

The effect of methoxyflurane on heart rate was variable and the figures are difficult to interpret as the control values were high, probably on account of the atropine and the lack of sedation. The average control value of 98 beats/min rose to 104, a difference which was not significant (0.10 > P > 0.05).

Mean arterial pressure was little altered by the inhalation of methoxyflurane and small decreases and increases were observed with no reproducible pattern. The average mean arterial pressure fell from 80 mm Hg to 78 mm Hg, a difference which was insignificant (0.30 > P > 0.20). The small deviations in mean arterial pressure induced by methoxyflurane anaesthesia were of the same order as those associated with the administration of halothane, and quite unlike the circulatory response to di-ethyl ether (fig. 1).

Normal sinus rhythm was present at all times during the studies except for minor alterations in the configuration of the P and T waves. Neither nodal rhythm nor ventricular ectopic contractions were noted. In the four children in whom cardiac rhythm was examined during periods of hypercarbia, ventricular extrasystoles accompanied

<table>
<thead>
<tr>
<th>Subject</th>
<th>Methoxyflurane (vol %)</th>
<th>Heart rate (per min)</th>
<th>Mean arterial pressure (mm Hg)</th>
<th>End-tidal Pco₂ (mm Hg)</th>
<th>e.c.g. (Methoxyflurane)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>Sex</td>
<td>Wt. (kg)</td>
<td>Control</td>
<td>Methoxyflurane</td>
<td>Control</td>
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<tr>
<td>10</td>
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<td>31</td>
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<tr>
<td>t = 1.88</td>
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<td>0.10 &gt; P &gt; 0.05</td>
<td></td>
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<tr>
<td>t = 1.27</td>
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<td>0.30 &gt; P &gt; 0.20</td>
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<tr>
<td>t = 5.83</td>
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<td></td>
<td>P &lt; 0.001</td>
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</table>

n.s.r. = normal sinus rhythm.
elevation of Pco₂ when halothane was being inhaled, while normal sinus rhythm persisted at all times during the administration of methoxyflurane. The results obtained in two of these children are shown in figure 2. In subject A idioventricular beats occurred during halothane anaesthesia when the Pco₂ was elevated to 65 mm Hg and, in contrast, normal heart action was maintained until the Pco₂ reached 87 mm Hg while methoxyflurane was being inhaled, at which level a return was made to normocarbia. In subject B comparable figures for Pco₂ were 71 mm Hg during halothane anaesthesia and 90 mm Hg when methoxyflurane was inhaled. A similar pattern was obtained in the other two subjects in whom methoxyflurane was administered before halothane.

**Respiratory changes.**

Although the increase in Pco₂ during the inhalation of methoxyflurane was small, this effect was noted in each of the ten subjects studied (table I). The average control figure of 40 mm Hg rose to 45 mm Hg when methoxyflurane was administered, this difference being significant (P<0.001). There was no overall correlation between the magnitude of carbon dioxide retention and the concentration of inspired vapour, but in individual children hypercarbia intensified as anaesthesia was deepened. Changes in respiratory rate and tidal volume associated with respiratory depression during methoxyflurane anaesthesia were not studied in this investigation.

**Blood sugar levels.**

Methoxyflurane caused little alteration in the blood sugar concentrations of the ten children studied, and the findings were not influenced by the subsequent surgery (table II).
DISCUSSION

The results show that alterations in arterial pressure during methoxyflurane anaesthesia resemble those of halothane rather than di-ethyl ether. Millar and Morris (1961) have observed that in the dog the levels of plasma catecholamines—adrenaline and noradrenaline—are not increased by methoxyflurane, so that hypotension is to be expected during anaesthesia with this agent. The fact that this new methylated ether, like halothane, failed to produce a significant fall in arterial pressure in the children studied may be due to heightened sympathetic responses in these small subjects, and the tachycardia which was invariably present during anaesthesia may reflect this increased activity. Unfortunately it was not possible to make measurements of plasma catecholamine levels and so confirm or refute this theory. In the adult, however, hypotension is frequently the rule when methoxyflurane is inhaled, and Walker, Eggers and Allen (1962) are of the opinion that this is primarily the result of a decrease in cardiac output. Bagwell and Woods (1962) suggest that although the fall in arterial pressure is of the same order with methoxyflurane and halothane, there may be a greater reduction in cardiac output and a smaller decrease in peripheral vascular resistance with the former. Detailed studies of peripheral vascular changes are required before this is established.

Although methoxyflurane is a halogenated compound which has been shown to sensitize the heart to adrenaline in the dog, several reports indicate that ventricular arrhythmias do not readily occur when clinically used concentrations of this anaesthetic are inhaled in man (Hudon, 1961; Power, 1961). The results of the present study show that normal sinus rhythm is maintained during uncomplicated methoxyflurane anaesthesia with Pco₂ within normal limits. This is to be expected since circulatory catecholamines are not elevated. It is well known that hypercarbia, by liberating excesses of these amines at the cardiac sympathetic nerve endings, may produce ventricular extrasystoles when a hydrocarbon is being inhaled (Price and his associates, 1958). In the present study, elevation of Pco₂ during the administration of methoxyflurane failed to initiate any disorders of cardiac rhythm. Although the data is limited, the implication is that the “Pco₂ arrhythmia threshold” for methoxyflurane, if there is one, is much higher than for halothane. It may well be that the ability of the former agent to sensitize the human heart to adrenaline is less than that of halothane. It has been shown by Israel, Dobkin and Robidoux (1962) that, in the dog, adrenaline-induced arrhythmias are less severe during methoxyflurane anaesthesia than when halothane is inhaled. Such considerations are in keeping with the clinical impression that
although respiratory depression is a feature of methoxyflurane anaesthesia, disorders of cardiac rhythm rarely occur.

Estimations of blood sugar concentrations made during the inhalation of methoxyflurane, both prior to and during surgery, reveal that there was no tendency to hyperglycaemia in the children studied. This is in accord with observations made by Millar and Morris (1961) in the dog, and also with their finding that this anaesthetic does not produce measurable increases in plasma adrenaline levels.

ACKNOWLEDGMENTS

We wish to express our thanks to the surgeons and theatre nursing staff of the Royal Belfast Hospital for Sick Children for their willing assistance and cooperation. We are most grateful to the staff of the biochemical laboratory of the Hospital for the estimations of blood sugar levels.

REFERENCES


