METHOXYFLURANE
A Clinical Study of Fifty Selected Cases

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SUMMARY
Fifty patients were anaesthetized using methoxyflurane, nitrous oxide and oxygen. Thiopentone enabled the induction time to be shortened. Respiratory depression particularly associated with reduction in tidal volume was observed. Hypotension was common and was often unrelated to depth of anaesthesia. There were episodes of bradycardia with hypotension. Muscle relaxation was good. Bleeding was diminished, no contraindication to the use of diathermy existed and adrenaline infiltrations were used without incident. Blood sugar levels were higher during anaesthesia and in the immediate postoperative period. Serum transaminase levels before and after anaesthesia indicate that methoxyflurane does not cause liver damage. The requirements of postoperative analgesics were considerably reduced. The incidence of postoperative nausea and vomiting was high. Protective reflexes were usually present at the end of operation but recovery of consciousness was greatly delayed.

A new anaesthetic agent, methoxyflurane (Penthane), 2-2 dichloro, 1.1 difluoroethyl methyl ether, has recently aroused considerable interest (Van Poznak and Artusio, 1960). A study of existing literature led the authors to believe that, although it may not be the ideal anaesthetic, it might be of value in procedures of comparatively long duration, where diminished bleeding was particularly desirable, and a speedy recovery was not essential. A clinical assessment of methoxyflurane anaesthesia was undertaken, and changes in respiration, blood pressure, blood sugar and serum transaminase levels were studied. In addition, the recovery time was noted, and the incidence of nausea and vomiting and the requirement of postoperative analgesics were recorded during the 48 hours following operation.

METHOD

The patients.
The mean age of the fifty patients studied was 41 years (range 12-69 years); thirty-six of the fifty patients were female. Seven patients had pre-existing hypertension, one chronic bronchitis, one asthma, one aortic stenosis, one had bilateral pulmonary secondary carcinoma, and one, with rheumatoid arthritis, was on long-term steroid therapy.

The series included all classes of surgery, with the exception of thoracic and neurosurgery, because in these early waking is considered to be of importance. The distribution is shown in Table I.

<table>
<thead>
<tr>
<th>Types of surgery performed in fifty patients.</th>
<th>Distribution of cases.</th>
</tr>
</thead>
<tbody>
<tr>
<td>General surgical</td>
<td>25</td>
</tr>
<tr>
<td>Gynaecological</td>
<td>7</td>
</tr>
<tr>
<td>Ophthalmic</td>
<td>7</td>
</tr>
<tr>
<td>Orthopaedic</td>
<td>6</td>
</tr>
<tr>
<td>Ear, nose and throat</td>
<td>5</td>
</tr>
</tbody>
</table>

The mean duration of anaesthesia was 74 minutes. No case lasted less than 35 minutes. The longest case, a total laryngectomy, lasted 44 hours.

Vaporization of methoxyflurane.
The trichloroethylene vaporizer on the Boyle apparatus was used. Methoxyflurane 100 ml was placed in the bottle, the lever fully opened, and...
the concentration of methoxyflurane vapour varied by raising or depressing the plunger. A total gas flow of 7 l./min was used in almost all cases. The vapour concentrations obtained were estimated by gas chromatography. The actual amounts employed are given in table II.

<table>
<thead>
<tr>
<th>Table II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentrations of vapour (vols. per cent) obtained with methoxyflurane 100 ml in trichloroethylene bottle of Boyle apparatus.</td>
</tr>
<tr>
<td>Temperature 20°C. Tap full open.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Position of plunger relative to surface of fluid</th>
<th>Gas flow</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 inch above</td>
<td>7 l./min 3 l./min</td>
</tr>
<tr>
<td>0.56–0.60</td>
<td>not estimated</td>
</tr>
<tr>
<td>Level</td>
<td>0.66–1.16</td>
</tr>
<tr>
<td>1 inch below</td>
<td>0.85</td>
</tr>
<tr>
<td>1.86–2.43</td>
<td>1.16</td>
</tr>
</tbody>
</table>

Anaesthetic technique.

Forty patients were premedicated with papaveretum 20 mg and hyoscine 0.4 mg. Eight older patients, were given pethidine 100 mg and atropine 0.6 mg. Two 12-year-old children were given papaveretum 10 mg and hyoscine 0.2 mg.

Other workers’ experience of the prolonged induction time with methoxyflurane (Artusio et al., 1960; Hudon, 1961; Andersen and Andersen, 1961; Power, 1961) led the authors to induce anaesthesia with thiopentone in all their patients. To eliminate any degree of airway obstruction, all cases were given suxamethonium and the trachea intubated. Intubation was preceded by 4 per cent lignocaine spray in 50 per cent of cases. Anaesthesia was maintained with nitrous oxide 5 l./min and oxygen 2 l./min. A Magill semi-closed system (Mapleson A) was used for all patients breathing spontaneously. A Radcliffe or Manley ventilator was used when ventilation was controlled. Initially a concentration of 1.5 per cent methoxyflurane was administered. This concentration was quickly reduced during the maintenance of anaesthesia.

Respiratory measurements.

During anaesthesia, in patients breathing spontaneously, the rate of respiration and the tidal volume were recorded at 5-minute intervals. Tidal volume measurements were made using a Wright respirometer.

Cardiovascular measurements.

The pulse rate and the systolic and diastolic blood pressures were recorded at 5-minute intervals. The blood pressure readings were obtained using an oscillotonometer.

Blood sugar estimations.

In twenty cases, blood samples were taken immediately prior to induction, after 1 hour of anaesthesia, at the end of operation, and 1 hour postoperatively. The true blood glucose levels were estimated by the glucose-oxidase method (Wincey and Marks, 1961). The normal fasting blood sugar values obtained by this method lie between 40 and 90 mg/100 ml.

Serum transaminase estimations.

In thirteen patients blood samples were taken immediately prior to induction of anaesthesia, and again 48 hours postoperatively. The serum glutamic oxalacetic transaminase and serum glutamic pyruvic transaminase levels were estimated by the colorimetric method described by Reitman and Frankel (1957).

Postoperative observations.

All patients were observed for 48 hours postoperatively. The ward nursing staff noted: the blood pressure at 20-minute intervals for at least 2 hours; the time the patient regained consciousness (this time was taken to be when the patient could answer a simple question); the occurrence of nausea or vomiting; the dose and time of administration of analgesic drugs.

In addition, nearly all patients were seen by the authors 1 hour postoperatively, and all were questioned at 48 hours as to nausea, unusual taste, or any other occurrence.

In order to discover any long-term complications, the follow-up notes on all patients were scrutinized not less than one month after operation.

RESULTS AND DISCUSSION

Anaesthetic technique.

Using thiopentone, a rapid induction was achieved, but it was soon discovered that inflation of the lungs with 1.5 to 2 per cent methoxyflurane was essential during the period of apnoea
following the suxamethonium. This prevented the patient coughing on the tube as spontaneous respiration returned, and enabled surgery to commence with minimal delay. No advantage was gained by spraying the larynx and trachea with 4 per cent lignocaine prior to intubation. Vapour concentrations of 0.5 to 1 per cent in nitrous oxide and oxygen were found satisfactory for maintenance of anaesthesia in most cases. The average rate of usage of methoxyflurane was 0.37 ml/min.

It was found that methoxyflurane did not stimulate pharyngeal or bronchial secretions. In most patients the pharynx was remarkably free from secretions at the end of operation. The pupils rapidly became constricted, fixed and central, and were of no value in judging the depth of anaesthesia. The patient's reaction to painful stimuli, the extent of fall in blood pressure, and the degree of muscle relaxation, were the main criteria used in assessing the depth of anaesthesia.

**Respiration.**

Respiratory depression was a constant feature of methoxyflurane anaesthesia. The tidal volume was reduced to approximately half the normal value [as predicted from the Radford nomogram], even with moderate anaesthesia. In five cases the tidal volume dropped to below half the normal value, and respiration was assisted. These findings agree with those of Hudon (1961) who recommended that pulmonary ventilation should in all cases be assisted or controlled.

In most patients the respiratory rate increased, the mean increase being 18 per cent (range +25 to +33 per cent). In ten cases ventilation was controlled from the outset. Control of ventilation was extremely easy to achieve. In all patients spontaneous respiration returned readily at the end of the operation.

**Cardiovascular system.**

Diminished bleeding during such operations as radical mastectomy and vaginal repair, was a noteworthy feature of methoxyflurane anaesthesia.

The mean maximum blood pressure change was a fall of 30 per cent (range 0 to 69 per cent), both systolic and diastolic, with a consequent reduction in pulse pressure. This fall in pressure was frequently noted during deep anaesthesia, but it also occurred in some patients only very lightly anaesthetized. It was not found to be as reliable a guide to depth of anaesthesia as other workers have reported (Artusio et al., 1960; Wasmuth et al., 1960; Hudon, 1961).

One patient developed a sudden fall in blood pressure to 65/40 mm Hg. This was rapidly corrected by mephentermine 10 mg intravenously. The pulse rate almost invariably fell, the mean change in rate for the series being a fall of 20 ± 14 per cent of the pre-anaesthetic figure. However, in 10 cases, a bradycardia of under 60 beats/min occurred, which was associated with a sudden fall in blood pressure. All responded adequately to atropine 0.6 mg intravenously. Clinically, no irregularity of the pulse was detected.

Infiltration with adrenaline in concentrations varying from 1:80,000 to 1:250,000 was safely performed in eight cases.

**Muscle relaxation.**

Relaxation for lower abdominal operations was very good. Six patients required no supplementary muscle relaxants. One was given gallamine 40 mg. Despite excellent muscle relaxation, sudden hard traction on the peritoneum occasionally caused a momentary contraction of the abdominal musculature. Jarman and Edghill (1963) also noted this effect. They stated that more reliable relaxation is obtained by thiopentone induction of anaesthesia, followed by maintenance with methoxyflurane, using a mask and drop bottle without endotracheal intubation.

**Effect on blood sugar.**

The true glucose levels in the blood, measured in twenty patients in whom adrenaline infiltration was not employed (thirteen breathing spontaneously and seven with controlled ventilation) showed a constant initial sharp rise, which continued more gradually during the second operative hour, and persisted into the postoperative period (table III).

The significances of the differences of the means have been obtained using Student's "t" test. In each case the value of P in table III refers to the comparison of the respective mean with the mean pre-operative value in that group. The
METHOXYFLURANE

TABLE III
The effect of methoxyflurane on blood glucose levels.
Mean values ± SD for true blood glucose levels expressed as mg/100 ml.
Range given in parentheses.

<table>
<thead>
<tr>
<th>Respiration</th>
<th>Pre-operative</th>
<th>After 1 hour's anaesthesia</th>
<th>At end of operation (mean duration of anaesthesia 105 min)</th>
<th>1 hour postoperatively</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controlled and spontaneous (20 patients)</td>
<td>65 ± 14.3 (42–112)</td>
<td>78 ± 13.9 (55–118)</td>
<td>81 ± 14.4 (54–115)</td>
<td>88 ± 20.2 (38–126)</td>
</tr>
<tr>
<td>Controlled (7 patients)</td>
<td>71 ± 18.7 (59–112)</td>
<td>87 ± 16.5 (66–118)</td>
<td>88 ± 13.4 (79–115)</td>
<td>102 ± 21.5 (67–126)</td>
</tr>
<tr>
<td>Spontaneous (13 patients)</td>
<td>61 ± 10.8 (42–76)</td>
<td>73 ± 10.4 (55–95)</td>
<td>78 ± 13.5 (54–112)</td>
<td>80 ± 16.3 (38–106)</td>
</tr>
</tbody>
</table>

results show that during methoxyflurane anaesthesia there is a significant rise in the true blood glucose level. The very similar increase during the first hour, in both spontaneous and controlled ventilation groups, led the authors to conclude that this hyperglycaemia is a true effect of methoxyflurane rather than a concomitant of hypercarbia associated with respiratory depression. This is likely to be due to release of catecholamines in a similar manner to that described for diethyl ether (Banerji and Reid, 1933; Minnitt, 1932; Robertson and Frazer, 1958).

The later rise in blood sugar during operation, was greater in patients breathing spontaneously than in patients in whom ventilation was controlled. Hypercarbia may be a factor influencing this secondary rise. The same explanation may account for the greater increase in early postoperative blood sugar levels which occurred in patients in whom ventilation had been controlled. One would expect these patients to be more deeply anaesthetized at the end of operation than those breathing spontaneously. In this case they would be more liable to respiratory depression in the immediate postoperative period. This supposition was indeed borne out by direct observation of these patients.

The rise in blood sugar during methoxyflurane anaesthesia is intermediate between the rise occurring during diethyl ether anaesthesia (Mekie, 1931; Drucker et al., 1959) and that occurring during halothane anaesthesia (Hunter, 1959). Gottlieb and Sweet (1964) found that in a series of ten cases anaesthetized with methoxyflurane there was no significant change in blood glucose levels. In their series no operative procedures were undertaken, and thus their results do not reflect the ability or otherwise of methoxyflurane to obviate the reflex release of catecholamines during stress. In addition, these authors were very careful to avoid any degree of respiratory acidosis by vigorously assisting respiration throughout. In the present series, in the majority of cases, ventilation was not assisted and, due to some carbon dioxide retention, may have produced a respiratory acidosis. As described by Morris and Millar (1962), even slight respiratory acidosis produces a considerable increase in catecholamine production.

Postoperative period.

Recovery time. The administration of methoxyflurane was discontinued, on average, 12.5 minutes before the end of operation. In all except four patients the laryngeal and pharyngeal reflexes had returned by the time of extubation but many of the patients remained unconscious for a long time.

Recovery time was defined as the time elapsing between extubation and the ability to answer a
simple question. The average for the series was 70 minutes, with a wide variation from 10 minutes to 4 hours 45 minutes. Fifty per cent of patients took more than 60 minutes to recover, while 25 per cent took more than 90 minutes (fig. 1).

Many workers have reported a wide variation in recovery time. Wyant, Chang and Rapicavoli (1961) found that if methoxyflurane had been used for induction as well as maintenance, the average waking-up time was 54.6 minutes. This could be reduced to 36.6 minutes by using thio- pentone for induction. Jarman and Edghill (1963) found that recovery time was lengthened if thio- pentone was used for induction. Denton and Torda (1963) noted recovery times varying from 10 to 200 minutes, with an average of 43 minutes.

The relatively long period in this series may be partly due to the fact that no operation lasted less than 35 minutes. Provided the duration of anaesthesia did not exceed 2 hours, however, little or no correlation was found between the duration of anaesthesia and recovery time. If the duration did exceed 2 hours, recovery time showed a sharp rise (fig. 2).

An interesting correlation appeared to exist between the patient’s weight and recovery time. This is shown in figure 3. These results are not quite significant at the 5 per cent level (r = -0.241; standard error ± 0.14). A certain amount of theoretical support for this relationship is given by the work of Chenoweth and associates (1961) on the blood and tissue distribution of methoxyflurane in dogs. They found that the concentration of methoxyflurane tended to increase in the fatty deposits of dogs, even after administration had been stopped. At the same time, the concentration in the blood fell and the animals began to wake, the blood levels falling more rapidly in the fat animals than in the lean ones.

Nausea and vomiting. There was a very high incidence of postoperative nausea and vomiting. Only 26 per cent of patients experienced no nausea or vomiting, 20 per cent experienced nausea alone, 34 per cent vomited once, and 20
per cent on more than one occasion. Nausea and vomiting was twice as frequent in women as in men. The high incidence in this series may be accounted for by the preponderance of female patients.

The average time of onset of either nausea or vomiting was just over 4 hours postoperatively. There was no emergence vomiting. In twelve cases the onset was delayed for over 12 hours, and in three cases, for over 24 hours. One patient had severe nausea and vomiting, which continued for six days. It ceased only when a large infected haematoma of the abdominal wound was drained.

Early reports quoted a low incidence of nausea and vomiting after methoxyflurane (Artusio et al., 1960; Wasmuth et al., 1960; Wyant, Chang and Rapicavoli, 1961), but some of these specified that the figures were for the immediate post-operative period only. Denton and Torda (1963), however, quoted an incidence of 60 per cent, and also commented that the onset was delayed in many of their patients.

Postoperative analgesia. It was the authors' impression that the requirement of postoperative analgesics was considerably reduced. In fact, 52 per cent of patients required no postoperative analgesia, 30 per cent needed one dose, and only 18 per cent of patients required two or more doses. In those patients requiring analgesics, 8½ hours elapsed, on average, before the first dose was needed. Most workers agree with this finding. Andersen and Andersen (1961), for example, found that their average time of administration of the first postoperative dose of analgesic was more than 5 hours after the end of operation.

Other postoperative observations. Twelve cases exhibited postoperative pallor. In only two of these was there associated hypotension. In nine cases, the systolic blood pressure fell by more than 15 per cent of the pre-operative value. In eight of these the duration of hypotension was less than 1 hour, and the systolic blood pressure was in all of them at least 75 per cent of the pre-operative level. In the remaining patient, upon whom a myomectomy had been performed, the systolic blood pressure fell from 120 mm Hg pre-operatively to 74 mm Hg. In this instance hypotension was due to postoperative bleeding, and required transfusion.

During the recovery period, two patients shivered, two patients showed shivering and rigidity, and six patients exhibited rigidity only. Seven patients complained of an unpleasant taste or smell.

Complications.

There was no mortality in the series. One patient, a female aged 50, with hypertension and a past history of a left uretero-nephrectomy for tuberculosis, had an uneventful vaginal hysterectomy. Three days postoperatively she developed septicemia, and became hypertensive and uraemic. She was dialyzed on the artificial kidney, and made a complete recovery. It was decided that her septicemia was sufficiently severe to account for her renal failure, and that methoxyflurane was almost certainly blameless. One patient had a mild chest infection. This was the only respiratory complication encountered. One patient developed an infected haematoma of her abdominal wound following abdominal hysterectomy. Another, after myomectomy, had a mild post-operative haemorrhage, and required blood transfusion. One patient had a unilateral recurrent laryngeal nerve palsy following thyroideectomy. There were no other postoperative complications.

Effect on the liver.

In thirteen cases the serum transaminase levels (serum glutamic oxalacetic transminase, normal range 0-25 units/ml, and the serum glutamic pyruvic transaminase, normal range 5-30 units/ml) were estimated pre-operatively and 48 hours postoperatively. The mean pre-operative s.g.o.t. level of 13 ± 6 units/ml rose to a mean value of 23 ± 11 units/ml. The mean s.g.p.t. level, originally 5 ± 4 units/ml, reached 7 ± 5 units/ml 48 hours postoperatively. In only one patient was a significant postoperative rise demonstrated. This patient had had an operation for shortening of the femur, which involved considerable muscle damage. The s.g.o.t. and s.g.p.t. rose from pre-operative levels of 18 and 11 units respectively to 51 and 20 units after 48 hours, and 54 and 40 units after 5 days. The serum bilirubin, however, remained less than 0.5 mg/100 ml, and he made an uneventful recovery.
ACKNOWLEDGMENTS

We are indebted to the surgical and nursing staff of King's College Hospital, London, for their willing co-operation; to our consultant anaesthetists for their encouragement and forbearance in allowing us to interrupt their lists for suitable cases; to Dr. M. J. H. Smith and his colleagues of the Department of Chemical Pathology for the blood glucose and serum transaminase estimations; and to Abbott Laboratories Ltd. for the supply of methoxyflurane and for performing the gas chromatography estimations.

REFERENCES


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METHOXYFLUORAN

Sommaire

Cinquante malades ont été anesthésiés par le méthoxyflurane, le protoxyde d’azote et l’oxygène. La phase d’induction a pu être raccourcie par le thiopentone. On a pu observer une dépression respiratoire particulièrement en association avec une réduction des volumes circulants. L’hypotension était fréquente et souvent sans rapport avec la profondeur de l’anesthésie. Il y avait des épisodes de bradycardie avec hypotension. Le relâchement musculaire était bon. Le saignement était diminué. On n’a rencontré aucune contre-indication à l’usage de la diathermie et les infiltrations d’adrénaline n’étaient jamais suivies d’incidents. La glycémie était augmentée pendant l’anesthésie et immédiatement après l’opération. Les taux des transaminases sériques avant et après l’anesthésie indiquent que le méthoxyflurane est atoxique pour le foie. Les besoins en analgésiques post-opératoires étaient considérablement réduits. La fréquence de nausées et de vomissements post-opératoires était élévee. Les réflexes de protection étaient en général présents à la fin de l’opération, mais le rétablissement de la conscience était en général considérablement retardé.

METHOXYFLUORAN

ZUSAMMENFASSUNG