METHOXYFLURANE

BY

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Methoxyflurane was introduced by Artusio et al. (1960) as a result of an examination of several different fluorinated hydrocarbon anaesthetics. Methoxyflurane is a fluorinated ethylmethyl ether with a chemical name of "2,2-dichloro-1,1-difluoroethylmethyl ether". Some of its properties are given in table I, together with comparative values for diethyl ether and halothane. From these figures it will be seen that methoxyflurane has a much lower saturation vapour pressure at ambient temperatures than these other agents. Consequently, the maximum concentrations attainable at normal operating room temperatures are approximately 3 per cent for methoxyflurane compared with approximately 30 per cent for halothane and approximately 60 per cent for diethyl ether.

Methoxyflurane is three times more soluble in blood than water, due to its affinity for the blood lipoproteins and haemoglobin. It has been suggested, therefore, that induction of anaesthesia is likely to be quicker in anaemic patients, as there is less haemoglobin for the vapour to dissolve into, and so the blood partial pressure of methoxyflurane will rise faster in such patients (Eger and Shargel, 1963). In fact, however, the amount taken up in other ways is relatively so great that the difference is not striking.

The very high oil/gas solubility ratio of methoxyflurane compared with halothane indicates that this agent is likely to have at least four times the narcotic potency of halothane, and that both induction and recovery will be prolonged.

Owing to the low volatility of methoxyflurane and the relatively low latent heat required for vaporization, the temperature of the vaporizer does not change materially when conventional gas flows are passed through it. This means that the vapour concentrations in the emergent gas stream are more likely to remain stable.

Methoxyflurane is non-explosive at normal operating room temperatures. It is stable on exposure to air, light and alkalis. It can, therefore, be used with soda lime in the circle system.

<table>
<thead>
<tr>
<th>Chemical formula</th>
<th>Diethyl ether</th>
<th>Halothane</th>
<th>Methoxyflurane</th>
</tr>
</thead>
<tbody>
<tr>
<td>C₆H₁₃-O-C₄H₈</td>
<td>CF₃-CHClBr</td>
<td>CHCl₃-CF₂-O-CH₃</td>
<td></td>
</tr>
<tr>
<td>Molecular weight</td>
<td>74</td>
<td>197</td>
<td>165</td>
</tr>
<tr>
<td>Specific gravity (liquid)</td>
<td>0.71</td>
<td>1.86</td>
<td>1.43</td>
</tr>
<tr>
<td>Boiling point (°C)</td>
<td>34.6</td>
<td>50.2</td>
<td>104.8</td>
</tr>
<tr>
<td>Saturated vapour pressure at 20°C (mm Hg)</td>
<td>442</td>
<td>241</td>
<td>25</td>
</tr>
<tr>
<td>Latent heat of vaporization (cal/gm)</td>
<td>87</td>
<td>35.2</td>
<td>49</td>
</tr>
<tr>
<td>Partition coefficients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Water/gas</td>
<td>13.5</td>
<td>0.74</td>
<td>4.5</td>
</tr>
<tr>
<td>Blood/gas</td>
<td>12.1</td>
<td>2.3</td>
<td>13</td>
</tr>
<tr>
<td>Brain/gas</td>
<td>17.3</td>
<td>5.4-8.3</td>
<td>22-30</td>
</tr>
<tr>
<td>Fat/gas</td>
<td>39</td>
<td>138</td>
<td>495</td>
</tr>
<tr>
<td>Oil/gas</td>
<td>64.8</td>
<td>224</td>
<td>825</td>
</tr>
<tr>
<td>Oil/water</td>
<td>3.8</td>
<td>330</td>
<td>400</td>
</tr>
<tr>
<td>Blood level for anaesthesia (mg/100 ml)</td>
<td>50-120</td>
<td>5-25</td>
<td>3-17</td>
</tr>
<tr>
<td>Arterial tension for narcosis (mm Hg)</td>
<td>14</td>
<td>7</td>
<td>1-1.5</td>
</tr>
</tbody>
</table>

Data for the partition coefficients has been obtained from Eger, Shargel and Merkel (1963), Larson, Eger and Severinghaus (1963), and Eger and Shargel (1963).
According to Hudon et al. (1963), liquid methoxyflurane forms a precipitate when in contact with copper, brass, bronze, and aluminium. In the vapour phase the agent does not react with metals. The vapour, however, is highly soluble in rubber (Eger and Brandstater, 1963) to about the same extent as in oil. Up to 60 per cent of the vapour may be lost to the rubber at the beginning of the anaesthetic when a fresh rubber hose is used. The higher the fresh gas inflow rate, the lower the percentage loss of vapour to the rubber. Conversely, when the vaporizer is turned off, methoxyflurane may still reach the patient (or subsequent patients) for several hours, as a result of its slow release from the rubber tubing.

**PHARMACOLOGICAL PROPERTIES**

**Neurological effects.**

The onset of anaesthesia with methoxyflurane is slow, as owing to the drug's low volatility and high blood solubility the brain tension of methoxyflurane rises very slowly. Analgesia is said to precede anaesthesia (Boisvert and Hudon, 1962). Methoxyflurane depresses the nervous system and, if enough of the drug is given, deep anaesthesia can be attained. Both the respiratory and vasomotor centres can be depressed easily but at normal anaesthetic concentrations of methoxyflurane, the amount of depression of these vital centres is slight.

Methoxyflurane, in terms of the partial pressure required for narcosis, which is of the order of 1 to 1.5 mm Hg, is the most potent anaesthetic available. The partial pressure of methoxyflurane in the brain which will produce anaesthesia is 1–1.5 mm Hg methoxyflurane. This may be compared with the 7 mm Hg partial pressure which is the partial pressure of halothane needed in the brain to produce narcosis (Nunn, 1963).

Just as induction of anaesthesia with methoxyflurane is slow, so is recovery from anaesthesia. Consciousness may not return for several hours after discontinuing the drug. This has been described by some as postoperative analgesia, but in fact it is more probably residual narcosis. The recovery time appears to be lengthened in proportion to the total length of anaesthetic exposure time.

**Cardiovascular effects.**

Apart from its tendency to produce hypotension the effects of methoxyflurane on the cardiovascular system are remarkably slight. The electrocardiogram and heart rate remain stable unless high concentrations of the drug are given for a long time. Then a bradycardia may develop. Ventricular irritability appears to be much less during methoxyflurane anaesthesia than during anaesthesia with other agents. In dogs anaesthetized with methoxyflurane there was a lower incidence of ventricular arrhythmias following adrenaline administration than occurred when the dogs were anaesthetized with many other halogenated hydrocarbon anaesthetic agents and then given adrenaline (Stephen, 1963).

The cardiac output is reduced slightly during methoxyflurane anaesthesia but the reduction in output is similar to that produced by halothane at comparable depths (Walker et al., 1962).

Plethysmographic studies show that the peripheral circulation remains unchanged during methoxyflurane anaesthesia (Payne, 1963), in contrast to the great increase in the forearm blood flow that occurs in halothane anaesthesia.

The blood pressure is depressed by methoxyflurane as a result of depression of the vasomotor centre. The hypotension is progressive if the inspired concentration remains unchanged; reducing the inspired concentration quickly reverses it. As with halothane, hypotension may occur early in anaesthesia, yet, when the patient is surgically stimulated, he will react briskly. Hypotension is directly related to the concentration of the drug in the blood stream.

**Respiratory effects.**

In the absence of opiate premedication, methoxyflurane produces rapid shallow breathing. This tachypnoea does not compensate for the reduced alveolar tidal volume and so the arterial Pa\text{O}_2 rises slowly. In the presence of opiate premedication there is no tachypnoea but the tidal volume is still reduced; therefore, respiratory depression is greater and the arterial Pa\text{CO}_2 rises faster unless the ventilation is assisted.

The respiratory reflexes are depressed early in methoxyflurane anaesthesia. Endotracheal intubation can be performed early in anaesthesia and the patient will tolerate the endotracheal tube, even when reacting to skin stimulation.
Muscular effects.

Muscular relaxation produced by 1.5 per cent methoxyflurane is not very profound, even after 1 hour’s administration of this concentration. The abdominal muscles may appear very relaxed with this concentration of methoxyflurane, but on slight stretching they may contract briskly. Many reports claim excellent muscle relaxation with methoxyflurane; however, in all these reports other drugs were also given.

Metabolic effects.

With methoxyflurane anaesthesia, a metabolic acidosis develops in addition to the slight respiratory acidosis. The reduction in standard bicarbonate after 1 hour of anaesthesia is about 1.5 m.equiv. This metabolic acidosis persists well into the postoperative period (Tomlin, 1963). One possible explanation is that since the peripheral circulation as measured in the forearm muscle mass is unchanged, redistribution of the circulating blood volume occurs to produce some tissue hypoxia, so leading to metabolic acidosis.

Liver function tests after methoxyflurane anaesthesia showed no toxic effect of any clinical significance (Jarman and Edghill, 1963). However, if there is marked elevation of the PaCO₂ during anaesthesia then severe liver disturbance, as judged by the bromsulphalein excretion test, may persist for several days (Morris, 1965). There has been one report of fatal liver failure after surgery in which methoxyflurane among other drugs had been given during anaesthesia (Lindenbaum and Leifer, 1963).

CLINICAL USAGE

There are now more than one hundred reports of clinical trials of methoxyflurane from various parts of the world. Earlier claims that methoxyflurane was a “complete anaesthetic”, capable of providing good anaesthesia when used as the sole agent, have now given way to more cautious recommendations suggesting that it should be used as a supplemental agent (McCaffrey and Mate, 1963).

All the commonly used drugs in modern anaesthetic practice have been given in the presence of methoxyflurane with no unexpected clinical problems. Respiratory depression is the most common complication occurring when methoxyflurane is given in the presence of narcotics. This depression may occur when the narcotics have been given as long as 2 hours before the premedication. For this reason it has been recommended that ventilation should always be assisted or controlled when methoxyflurane is being given (Wyant et al., 1961).

The most notable feature of the clinical reports has been the stability of cardiac rhythm reported in patients given methoxyflurane. Hypotension is easily reversed by reducing the inspired methoxyflurane concentration and bradycardia will respond to atropine. Pallor is another feature which has been frequently described, particularly in the earlier reports; it may persist into the postoperative period. The significance of the pallor is unknown.

Emergence from anaesthesia is slow. The amount of postoperative medication required after methoxyflurane anaesthesia appears to be less than with other agents. The incidence of postoperative vomiting after methoxyflurane anaesthesia is said to be slight (McIntyre and Gain, 1962), and to be comparable to that following halothane (Chang et al., 1957). Even in obstetrics the incidence of postanaesthetic vomiting is comparable to that following halothane given to a similar group of patients (Boisvert and Hudon, 1962). Other workers, however, regard methoxyflurane as a relatively frequent cause of postoperative vomiting, though no worse than halothane (Munro, 1963).

DISCUSSION

The physical properties of a vapour determine how it behaves when it is used in anaesthesia. They determine how useful the drug is, how controllable it is, and what its limitations are. Methoxyflurane is a good example of how the physical properties of a drug seriously limit its usefulness. The drug has a low saturation vapour pressure and in addition, is rapidly absorbed by rubber. As a result, induction time is long. The induction time can be shortened by using a calibrated vaporizer which will produce a saturated vapour and through which all the fresh gas flow can be diverted if necessary. The use of high gas flows during induction will reduce the importance of rubber adsorption.
However, there remain the twin problems of methoxyflurane's high blood solubility and low volatility. Inevitably, because of this, control of the arterial vapour partial pressure, and therefore control of anaesthesia, will remain unwieldy compared to the fine degree of control attainable with other drugs. Induction will be slow, changing from one level of anaesthesia to another will be slow, and recovery will be slow. The lack of flexibility consequent upon methoxyflurane's high blood solubility is the chief drawback to its use in anaesthesia. The high potency of methoxyflurane consequent upon its high oil-gas solubility ratio compensates little for the disadvantages resulting from its high blood solubility and low volatility.

Ether is the only other anaesthetic vapour in common use which has a similar blood solubility to methoxyflurane. It also has a much lower oil-gas solubility and so is less potent than methoxyflurane. However, its volatility as indicated by its saturation vapour pressure at room temperature is twenty times greater than methoxyflurane. As a result, much more can be given at any particular time and so the blood level can be raised easily to anaesthetic concentrations. If ether had the same relative saturation vapour pressure as methoxyflurane, it would be almost impossible to induce anaesthesia with it.

The principal advantages of methoxyflurane are that it is non-irritant to the myocardium compared with trichloroethylene and halothane, that endotracheal tubes are tolerated in light levels of anaesthesia, and that it is easier to maintain the level of anaesthesia constant.

REFERENCES


