METHOXYFLURANE

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METHOXYFLURANE is one of a large number of fluorinated hydrocarbons and fluoroethers that have been studied in recent years.[1,2] This compound is 2,2-dichloro-1,1-difluoroethyl methyl ether, and is marketed under the name Penthrane, Abbott. It is non-explosive in the concentrations used clinically and at the temperatures encountered. Other physical properties of the drug are illustrated with those of other commonly used volatile anaesthetic agents in Table I. The drug has a lower latent heat of vaporization than water and consequently vaporizes more readily in spite of its higher boiling point. A high

TABLE I

	Diethyl ether	Methoxyflurane	Halothane
Boiling point (°C.) at 760 mm. Hg	34 6	104 8	50 2
Specific gravity at 20°C.	0 71	1 42 (at 25°C)	1 86
Vapour pressure in mm. Hg at 20°C.	442 0	25	241 5
Oil-water distribution coefficient	3 8	400 0	330 0

oil–water distribution coefficient is usually associated with potency but in spite of this fact the very low vapour pressure of methoxyflurane makes elaborate vaporizer safeguards unnecessary and the administration relatively safe.

Since 1960 several accounts of the clinical use of the drug have appeared,[3,4,7] and this report is intended to supplement these.

A closed or semiclosed circle absorber system was commonly used and the methoxyflurane was introduced either by placing a Heidbrink No. 8 ether vaporizer containing 80 ml. within the circle on the inspiratory side, or by using a 2 litre per minute gas flow (N_2O:O_2 1:1) over 175 ml. in the Boyle ether vaporizer outside the circle. When used in the latter vaporizer the total gas flow was directed through the vaporizer and the concentration varied by altering the plunger position from fully elevated to a point producing maximal surface agitation and minimal bubbling. The relationship of the lower end of the plunger to the millilitre markings on the bottle indicated the intermediate settings. In an attempt to determine the concentrations produced at these settings the volume of methoxyflurane volatilized by a 2 L./min. gas flow for one hour was measured in six vaporizers. The operating room temperature was 21° C. and the humidity 45 per cent. Clinical experience indicated that substantial volumes were still being vaporized after 3 to 4 hours use.

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MINIMUM RECORDED	MAXIMUM RECORDED	AVERAGE RECORDED%
0.97	1.13	1.0
1.13	1.34	1.3
1.13	1.40	1.3
1.40	1.58	1.5
2.68	3.35	3.0

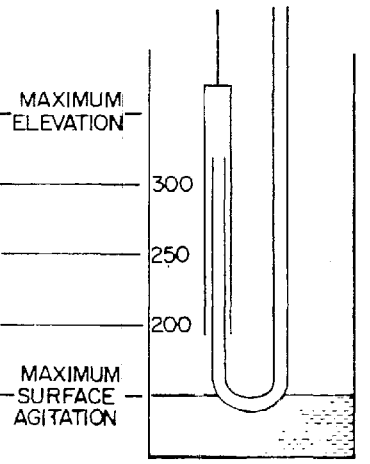

FIGURE 1

Induction of anaesthesia with this drug alone is slow and the use of an intravenous agent or heavy sedation was considered mandatory. The odour is persistent and unpleasant to some people; consequently circuits with high flows were used only when provisions could be made for the removal of expired gas from the operating room. With these reservations in mind it has been used routinely for a variety of unselected cases (see Table II).

TABLE II

Orthopaedic	70
Neuro	15
Gynaecologic	55
General surgical	215
Thoracic	20
Cardiac	
Open	14
Closed	10
Miscellaneous	62
Total	461

Using a maximum induction dose of thiopentone of 400 mg. it was found that the rapid introduction of methoxyflurane necessary to produce analgesia by the time the skin incision was made occasionally produced laryngeal irritation. In cases where this was anticipated succinylcholine 40 mg. was given intravenously following the thiopentone, and artificial ventilation was begun immediately.

Methoxyflurane alone facilitated the introduction of controlled ventilation in cases suffering from all varieties of pulmonary pathology. Although many patients could ventilate themselves adequately, it was observed in some cases that there was marked depression of respiration before the depth of anaesthesia was sufficient to prevent response to the skin incision.

Succinyldicholine, decamethonium, gallamine, and *d*-tubocurare are all compatible with this agent and, as with other anaesthetics, the dosage required varies with the degree of central depression. Methoxyflurane alone produces moderate relaxation but not sufficient for the more exacting surgeon. Most lower abdominal

procedures can be performed without the use of relaxants if controlled respiration is used, anaesthetic levels that depress circulation not being required.

No arrhythmias were encountered and no existing ones aggravated. Serious bradycardia unrelated to a reflex stimulus did not occur. Anaesthetic concentrations produced a small fall in blood pressure but no patient could be described as being unable to tolerate the drug. For one case, 10 ml. 1 per cent procaine, 1:300,000 epinephrine was injected into the vaginal wall. This produced a very irregular pulse for three minutes, which suggests that this combination must be used with considerable caution if at all.

Chenoweth[11] reports that the blood concentration during methoxyflurane anaesthesia rises steadily for the first two hours and very slowly thereafter. After approximately three hours the concentration of methoxyflurane in the fatty tissues is the same as in the blood, but the concentration in the fat continues to increase. Shortly after methoxyflurane is discontinued the blood level falls rapidly, but the fat concentration will continue to increase for about two hours even though the blood concentration is falling. This would then explain the apparent paradox of a more rapid recovery of the large, obese patient than one would otherwise expect. Similarly the lean, thin type has a more prolonged recovery.[6] In this series the administration of methoxyflurane was stopped 15–20 minutes before the termination of surgery and a semiclosed circuit with high gas flows used. The average time spent in the recovery room for 300 patients was 60 minutes.

Discussion

Chloroform was the first halogenated hydrocarbon to be used extensively in anaesthesia and recently halothane has become the most widely accepted anaesthetic within this chemical group. These two drugs have a high saturated vapour pressure (chloroform 160 mm. Hg, at 20° C., halothane 241.5 mm. Hg at 20° C.), and precision vaporizers are necessary for their safe administration. Perhaps this is no great disadvantage in a technological age, but nevertheless the simplicity of equipment necessary for vaporizing a drug of low saturated vapour pressure such as methoxyflurane (25 mm. Hg at 20° C.) does seem a significant safety factor. An increase in induction time might be anticipated but can be avoided by the use of thiopentone and neuromuscular blocking agents, and in practice presented no problem.

Experimental work on dogs has demonstrated certain similarities and dissimilarities between methoxyflurane and halothane. Using 2 per cent halothane and 1 per cent methoxyflurane Dobkin (8) found that the mean arterial pressure decreased more with halothane than with methoxyflurane. Both drugs slowed the pulse, and the cardiac output fell more with halothane. With augmented breathing the depressant effect on blood pressure, pulse, and cardiac output were not significantly different. Millar[4] stated that after 2 per cent halothane and 0.55–0.78 per cent methoxyflurane the average mean arterial blood pressure levels were about the same, and, as for halothane, the plasma adrenaline and noradrenaline levels were not significantly increased. The increase in total catecholamine level resulting from haemorrhage or hypercarbia during methoxyflurane anaesthesia was less than those previously measured with halothane and

could be interpreted as an indication of greater suppression of central or peripheral reflex sympathoadrenal responses with methoxyflurane than with halothane. The consistent bradycardia that occurred with halothane did not appear with methoxyflurane.

Respiration was depressed more by methoxyflurane than by halothane.[8] Dobkin found no gross differences in electrolytes, blood sugar, cephalin-cholesterol flocculation that might reflect differences in metabolic changes or alterations in liver function.[8] North reported that the liver findings after 1 per cent methoxyflurane for three hours were similar to those after halothane.[9] Dobkin[10] found that the arrhythmias provoked by an epinephrine challenge during 1 per cent methoxyflurane anaesthesia were less severe than those seen during similar experiments with halothane. However, in view of the cardiac arrhythmias produced, caution was advised with this combination of drugs.

The concentration of methoxyflurane used in the clinical series presented was probably slightly higher than that often used experimentally. However, many of these findings were confirmed. Bradycardia was infrequent, and in contrast to halothane, intravenous atropine was never required. Severe fall in blood pressure due to the drug rarely occurred, and it was easily reversed by reducing the concentration. The blood pressure was sometimes reduced by 10–20 mm. Hg and the impression was that it was less depressant than halothane. Certainly administered with the vaporizer in the circle it was not associated with the severe fall in blood pressure sometimes produced by the latter drug.

Methoxyflurane had a respiratory depressant action that rendered it unsuitable for use when unassisted ventilation with rapid obtundation of upper respiratory tract reflexes was required, contrasting in this respect with halothane. Nevertheless the respiratory depression was not as marked as some of the literature would lead one to believe.

Observation of 50 comparable orthopaedic cases in the recovery room showed that restlessness was less frequent after methoxyflurane than halothane and that the patients were drowsier. A similar number in each group actually received analgesic drugs. The use of sedative and analgesic drugs in the recovery room prolongs the time spent there, and the average sojourn of 300 general surgical cases was 60 minutes after methoxyflurane and 55 minutes after halothane.

The prophylaxis in the operating room of postoperative restlessness and pain or its active treatment in the recovery room is a valuable method of assessing the effect on each patient of drugs that will be used subsequently in the ward. The safe use of an anaesthetic drug, which by its slow excretion produces a slow and peaceful recovery, is dependent on meticulous nursing and medical care during the first few hours postoperatively. The slowly excreted drug may potentiate the effects of cardiovascular failure or respiratory depressant drugs, thus delaying further its own elimination, and producing a deterioration in the condition of the patient. No complications attributable to this occurred in the series presented, but this might not have been the case had not good recovery room care been available.

The incidence of postoperative vomiting is an important feature to consider in assessing the possible value of any new anaesthetic agent. The low incidence

of vomiting with halothane was an important factor in the acceptance of this agent. In this series, of the 165 unselected cases anaesthetized by one author (E. A. G.) all were given the usual opiate and belladonna medication preoperatively. Four patients vomited in the recovery room. None of these vomited after return to the ward. Four patients vomited on the ward. One of these was a child and the other three were adults. Of these three adults, two had received opiates postoperatively before the vomiting occurred. It would appear that this agent produces a remarkably low incidence of nausea and vomiting.

Conclusion

Methoxyflurane is non-inflammable and non-explosive at room temperature, comparable with soda lime, and can be used for general anaesthesia in a vaporizer of simple design. It can be administered most economically in a closed circuit, and the vaporizer can be used safely within the circle. The drug is satisfactory under almost all circumstances but its slow absorption, respiratory depressant effect, and odour make it unsuitable for a minority of cases. It provides marked analgesia, good muscular relaxation, and a remarkably low incidence of vomiting. With the exception of depression of respiration, and incompatibility with epinephrine, this agent exhibits all of the advantages and none of the disadvantages of diethyl ether with an even greater margin of protection from overdose.

Résumé

Le méthoxyflurane est non inflammable, non explosif à la température de la salle, utilisable avec la chaux sodée et on peut s'en servir comme anesthésique général en employant un vaporisateur ordinaire. On peut l'employer très économiquement dans un circuit fermé et le vaporisateur peut être placé en toute sécurité dans le circuit. Ce produit donne satisfaction dans presque toutes les circonstances, mais son absorption lente, son effet dépresseur de la respiration et son odeur le rendent peu pratique dans un petit nombre de cas. Il produit une analgésie marquée, un bon relâchement musculaire et très peu de vomissements. A part ses effets dépresseurs sur la respiration et son incompatibilité avec l'épinéphrine, cet agent anesthésique présente tous les avantages et aucun des désavantages de l'éther éthylique et possède contre le surdosage, une marge de sécurité encore plus grande que celle de l'éther.

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