METHOXYFLURANE*

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METHOXYFLURANE is 2,2-dichloro-1,1-difluoro-ethyl methyl ether with the formula

$$CH_3\text{-}O\text{-}CF_2CHCl_2.$$

It is a clear, colourless liquid of characteristic odour which boils at 104.8° C. The vapour pressure is approximately 25 mm. Hg at 20° C. The vapour pressure of water is 17.5 mm. under the same conditions. The greater vapour pressure of methoxyflurane is explained by the latent heat of vaporization which is 49 calories per gm. compared to 540 calories for water. The compound is stable in the presence of light and does not react with soda lime.[1]

The explosive limits are approximately 4 per cent at 60° C. At room temperature it is nonflammable in any concentration of air, oxygen and nitrous oxide. Vapour density is 7.36 g/l. Its water solubility is 0.22 grams/100 grams. Its behaviour is in many ways similar to that of diethyl ether and Fluothane. It can be administered by any technique: open drop, semi-closed and closed circle. A precision vaporizer is not essential, but is much safer.

In calculating the concentration of methoxyflurane in a copper vaporizer, one must remember that the vapour pressure of methoxyflurane is one-tenth that of Fluothane, that is to say, 25 mm. Hg compared to 250 mm. in usual conditions.

Clinical Considerations

Loss of consciousness and automatic respiration are achieved in a period from two to four minutes, but at this time the patient will still react to painful stimuli. Induction time with open drop or N_2O/Penthrane‡ takes from eight to twelve minutes in adults, from six to eight minutes in children, but less following thiopentone induction. Intubation time is shorter with the use of a muscle relaxant drug.

If intubation is carried out after thiopentone induction and the use of a short-acting muscle relaxant, it must be realized that the patient will not always be saturated enough to tolerate the endotracheal tube, in spite of the fact that analgesia is sufficient.

A small dose of succinylcholine chloride administered after 2 mg. of decamethonium allows sufficient time for saturation with methoxyflurane. A 1.5 per cent concentration of methoxyflurane is sufficient to achieve surgical anaesthesia. Induction is begun with this concentration and the concentration is maintained until surgical anaesthesia is obtained. Patients will cough on higher concentrations.

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‡The name given by Abbott Laboratories Ltd. to methoxyflurane is Penthrane.

The maximum concentration obtained under normal conditions is a little over 3 per cent. Maintenance is easy and smooth with a concentration of 0.5 per cent.

With the Vernitrol vaporizer specially calibrated for us with an oxygen scale of three litres, induction and maintenance present no problem for both re-breathing and non-rebreathing techniques. Even with a ten-litre flow of diluent gas, one may attain a little more than 0.7 per cent concentration at 20° C. temperature.

The usual Vernitrol vaporizer, which is calibrated with an oxygen scale of one litre, necessitates a low flow of diluent gas to reach 1.5 per cent concentration of methoxyflurane. A flow rate of one litre from the vaporizer combined with a flow rate of three litres of diluent gas gives a 0.8 per cent concentration of methoxyflurane. This low-flow technique is used with soda lime in semi-closed circuit. As it prolongs the induction, we have to resort to an induction with another general inhalation anaesthetic or a thiopentone, curare, nitrous oxide sequence.

Therefore, four litres of diluent gas will permit the administration of a 0.62 per cent concentration of methoxyflurane as one litre of oxygen passes through the vaporizer.

This concentration is maintained from ten to fifteen minutes and decreased to 0.4 and then to 0.3 per cent according to the length of anaesthesia and the amount of drug accumulated in the bag and in the patient's tissues as re-breathing occurs.

The technique which we have developed, using the Heidbrink Kinetometer equipped with the ether vaporizer bottle No. 8 in the inspiratory side of the circle, is as follows. The anaesthetic agent is vaporized with a flow rate of four litres, two of nitrous oxide, two of oxygen, and the vaporizer of the circuit opened at the No. 4 setting. This gives a concentration of a little over 1 per cent. After induction, the anaesthetic agent is delivered at the No. 2 setting, giving a concentration of about 0.5 per cent. For long operations, No. 1 setting gives sufficient analgesia.[2]

This is not an accurate technique, since the opening of the bottle is not made with precision. The concentration varies with the minute volume and with the control of respiration. It also varies as water of condensation accumulates above the anaesthetic agent. However, it is a satisfactory method, but requires considerable attention in following the signs of anaesthesia. Furthermore, some patients become too saturated at the end of the operation and sleep longer. In the non-rebreathing technique with high flow of gas, the dial must be set at No. 8 for induction and lowered to 6 for maintenance.

The following technique is adopted with the Boyle's machine. The drug is poured into the Azeotec or Fluotec vaporizer and also into the bottle of the circle. The Azeotec fully opened delivers one-tenth the concentration of methoxyflurane as compared with fluother, that is 0.45 per cent of methoxyflurane. To obtain 1 per cent more concentration, the bottle of the circle is opened at the same time at setting No. 5 with a gas flow of four litres. For induction, these two vaporizers are used together with a gas flow of four litres. For maintenance, the Azeotec vaporizer is kept open. With non-rebreathing technique, the tube to the patient

is connected on the inspiratory side of the circle, where the vaporizer is, and the openings of the expiratory side and of the bag are closed. In this manner, one or both vaporizers may be used. In obstetrics, the Azeotec or Fluotec vaporizer alone is sufficient in the semi-closed technique.

Nausea and vomiting do not occur during induction. Delirium or excitement rarely occurs. Methoxyflurane is a potent anaesthetic, and induction is safe because of a low vapour pressure and delayed saturation of the tissues. However, the administration of the drug must be adjusted to a known and safe level when the surgical anaesthesia is established, since the blood pressure may fall quickly in the third plane of the third stage.

A precision vaporizer outside the circle assures light anaesthesia without fluctuation. At low concentrations analgesia is sufficient, and blood pressure very stable even in the reversed Trendelenburg position.

Respiration

During open drop methoxyflurane or $N_2O + O_2 +$ methoxyflurane induction, there is little change in minute volume, but as we reach the surgical stage some depression of the respiration occurs.[3] Respiration is depressed after thiopentone induction. During surgical anaesthesia, minute volume is often decreased by half, as we observed with the Wright ventimeter.

Respiration must be assisted or controlled during induction, maintenance and recovery. Resistance to respiration is minimal. No increase in salivary activity or mucus secretion has been observed at any time. Patients operated on for cleft palate or rhinoplasty show less postoperative secretions and are more comfortable than after the use of other general anaesthetics. Pharyngeal reflexes are depressed early. Once saturation is adequate, the endotracheal tube is tolerated well.

Circulation

Blood pressure stays within normal limits during induction and maintenance, but may fall in deep anaesthesia.

Generally, fifteen minutes will elapse from the start of the anaesthetic before there may be a fall in blood pressure. When thiopentone is used for induction, one must watch for the depression of the circulation which is produced by the latter drug and, as anaesthesia proceeds, one must wait so as to allow the organism to recover from this inhibition.

A lowered blood pressure usually means overdose of methoxyflurane. This action can be reversed quickly by decreasing the concentration of the drug. The cardiac rate is stable. A large series of cases were followed with the electrocardioscope. Once, a severe ventricular arrythmia was seen in a child. A wandering pace-maker appeared in a small proportion of cases. The P wave became flattened or absent. Occasionally, a nodal rhythm was seen.[4]

Bamforth *et al.* found methoxyflurane similar to chloroform in sensitizing the heart of dogs to epinephrine.[5] Other investigators have found that epinephrine given intravenously, even in large doses, did not cause cardiac fibrillation while methoxyflurane was being used.

According to Stephen, it is more difficult to induce ventricular fibrillation in dogs with this drug than with other previous anaesthetics known to sensitize the heart to epinephrine.[6]

Epinephrine was injected in thirty of our cases to overcome oozing. The dose used was one drop of epinephrine at 1:1000 dilution mixed with five cc. of novocaine 1 per cent. One to 5 cc. of this solution was injected. This represents a dose of 0.001 to 0.002 mg./kg. as compared with 0.01 and 0.05 mg. injected intravenously in dogs by Bamforth *et al.*

All of these patients were followed on the electrocardioscope, except for five babies with cleft palate, and none developed arrythmias. An occasional wandering pace-maker was seen.

Muscular Relaxation

Masseter muscles relax early. Methoxyflurane produces a good quality of muscular relaxation. However, small doses of relaxants allow surgical maintenance with light levels of anaesthesia and, accordingly, a more stable blood pressure level.

Gastro-intestinal System

Nausea or vomiting appears neither during induction nor during fluctuations of the level of anaesthesia. A total of 410 patients were followed in the recovery room on a double-blind control in comparison with fluother. Of the patients 4.5 per cent vomited in the recovery room, 13 per cent had nausea. At the same time, of 169 patients who were given fluother, 7 per cent vomited, 10 per cent had nausea. These patients were premedicated with Meperidine-Atropine and occasionally Benadryl.

In the postoperative period, obstetric cases excluded, 17 per cent had slight nausea or vomiting the first or the second day, according to the records.

Emergence Recovery

The administration of methoxyflurane is decreased to a 0.2 per cent concentration prior to the end of the surgical procedure. After long operations, the endotracheal tube is left in place in the recovery room and connected, as respiratory depression occurs, to an automatic respirator. Recovery is quiet and is more prolonged than after fluother.

Awakening occurs generally in less than fifteen minutes. After long and deep anaesthesia, some patients are depressed for one or two hours and answer questions slowly and with difficulty. As more experience is gained and more precise techniques are used, these cases will be exceptional.

Injection of prostigmine and atropine is tolerated well. Vanillic diethylamide in doses of 1 or 2 mgm. per pound of body weight stimulates depressed respiration and awakens the patients to a certain degree.

Obstetrics

Methoxyflurane was used in 144 obstetric cases. $N_2O + O_2$ and methoxyflurane in semi-closed technique acts very quickly. A 0.5 per cent concentration

is sufficient to obtain sedation and analgesia in a few minutes. Uterine contractions continue in light planes of anaesthesia. Babies cry spontaneously. Generally, no nausea or vomiting appears even after the injection of ergot derivatives. In this small series, neither abnormal haemorrhage nor uterine inertia occurred. Three patients vomited in the awakening period, five vomited a few hours later.

Discussion

Methoxyflurane was used in 939 cases, without consideration of the type of operation, but especially in long operations and cancer cases. Premedication consisted of one injection of Meperidine and Atropine. A small percentage also received Benadryl. N_2O + O_2 + methoxyflurane induction was achieved in 25 per cent of cases.

An induction with N_2O + O_2 + fluother, or a sequence consisting of a small dose of thiopenthane, decamethonium, succinylcholine chloride for intubation followed by N_2O +O_2 + methoxyflurane were used for the other cases. Small doses of nondepolarising curare may be used at intervals during maintenance. High flow technique was used in children with a mask, or Ayre's technique, or even at the tip of a bronchoscope, in 0.8 per cent concentration for maintenance. Semi-closed technique with soda lime is used in adults.

Respiration is *always* assisted or controlled. A precision vaporizer is preferable. Open drop method was used in several children. Just a few drops are sufficient to put babies to sleep with safety. The signs of anaesthesia as observed consisted in the movements of limbs, tears, conjunctival and corneal reflexes, blood pressure level and the concentration of the drug. Pupils are small and their interpretation is difficult. The conjunctivae are congested.

No cardiac arrest occurred. Methoxyflurane caused less vomiting than ether and cyclopropane. After abdominal surgery, 6 5 per cent of the cases had pulmonary complications consisting of cough and expectoration. One patient developed a consolidation of the lower right chest and pleural effusion after a left thoraco-abdominal incision. He was re-operated on for an oesophago-gastric fistula.

Another patient, 76 years of age, two weeks after a gastrectomy for ulcer, developed a parotitis and an atypical pneumonia as diagnosed by radiography. A tracheotomy was needed as part of the treatment to control the pulmonary infection. The patient was anaesthetized a third time with methoxyflurane for incision and drainage of the parotid.

Other complications were benign in nature. The incidence of pulmonary complications is lower than with other inhalation anaesthetics as studied in the previous years in our series. Bacteriological studies were done by Dr. André Potvin, supposing that cross infection by the machine could be decreased. Methoxyflurane and halothane were found bactericidal for some micro-organisms. Ether has a bacteriostatic action on the same micro-organisms. In the month following surgery, eight patients died. Five of them died of normal evolution of their cancer, one of gastric haemorrhage, one of peritonitis and one of the complications of a cirrhosis of the liver. Three of them had biopsies of the

TABLE I

SUMMARY OF EXPERIENCE WITH METHOXYFLURANE

	Cardiac arrest	Nausea in recovery room	Vomiting in recovery room	Nausea and vomiting postop.	Postop. pulmonary complications	Postop. mortality
Total: 939 cases	0					8
Obstetric cases: 144	0		3 cases	5 cases		0
Obstetric cases excluded: 795				17%		
Laparotomies: 265 cases					6.5%	8
Double control in recovery room:						
PENTHRANE: 410 cases		13%	4.5%			
FLUOTHER: 169 cases		10%	7%			

liver during the operation and at autopsy as well. There was no difference between the two biopsies except in the patient who died of complications of a cirrhosis of the liver. A porto-caval shunt had been performed five days before. An autopsy done by Dr. Jean-Louis Bonenfant, after confirming the finding of a cirrhosis with esophageal varices, proved the porto-caval shunt to be intact and patent. Microscopically, there were minute foci of hepatic necrosis, ischaemic in type, suggesting a failure of the hepatic artery blood flow to oxygenate the liver cells, owing to the massive porto-caval shunt. However, parenchymal involvement of other organs (spleen, pancreas, kidneys) was conspicuously absent.

Another patient had a biopsy of the liver during a gall bladder operation. Histological examination showed fatty cirrhosis of the liver in its initial phase. This patient has had a trouble-free postoperative course and left the hospital ten days later in very good condition.

SUMMARY AND CONCLUSION

Methoxyflurane (Penthrane®) is a new halogenated anaesthetic agent. Induction is slow but smooth. This may be considered as a safety factor. It provides good muscular relaxation. Cardiac rhythm remains stable, so that it may probably be used with epinephrine; our clinical experience confirms that point.

Respiration is depressed by half. Recovery may be prolonged by overpremedication, deep anaesthesia and hypoventilation.

Employed in combination with other anaesthetic agents and curare, and delivered with a precision vaporizer, methoxyflurane permits a faster recovery. Awakening is quiet and without hypotension.

As this drug seems no more toxic than the other inhalation anaesthetic agents it could be useful in anaesthesia in general and in obstetrics in particular.

Résumé

Le Penthrane® est un nouvel agent anethésique halogéné. Il s'administre par inhalation avec les vaporisateurs ordinaires, mais de préférence avec un vaporisateur de précision.

Il est non explosif à la température de la chambre et non affecté par la chaux sodée.

L'induction est douce, mais lente. L'administration de Pentothal-succinylcholine-protoxyde d'azote-oxygène suivie de Penthrane rend l'utilisation de celui-ci plus satisfaisante.

La respiration est déprimée, la pression artérielle baisse en anesthésie profonde. Le rythme cardiaque est stable et n'est pas influencé par de faibles doses d'adrénaline injectées dans les tissus.

Associé au protoxyde d'azote, le Penthrane en concentration de 0.5 pour cent suffit pour la maintenance en circuit semi-fermé.

Le relâchement musculaire est bon en anesthésie profonde, mais de faibles doses de relaxants sont suffisantes et préférables à l'anesthésie profonde qui amène une chute de pression. Les signes de l'anesthésie sont plus difficiles d'interprétation, ce qui oblige à suivre le niveau de la pression artérielle et à utiliser des vaporisateurs précis plaçés en dehors du circuit.

Le réveil est calme, mais prolongé si la prémédication a été trop forte et si la saturation est trop marquée.

Les vomissements sont rares.

En obstétrique, le Penthrane associé au protoxyde d'azote fournit une sédation et une analgésie d'apparition rapide. L'expulsion continue, le bébé se comporte normalement, la parturiente ne vomit pas et ne présente pas d'inertie utérine. La dose employée est minime et l'accouchée se réveille en moins de cinq minutes.

REFERENCES

1. Artusio, Joseph F., Jr., *et al.* A Clinical Evaluation of Methoxyflurane in Man. Anesthesiology *21*: 512-517 (1960).
2. Van Poznak, Alan *et al.* Methoxyflurane as an Anesthetic Agent. Cleveland Clin. Quart, *27*: 174–183 (1960).
3. Siebecker, Karl L., *et al.* The Respiratory Effects of Methoxyflurane (DA. 759 Abbott) on Dog and Man. Anesthesiology *22*: 143 (1961).
4. North, William C. et al. Respiratory, Circulatory and Hepatic effects of Methoxyflurane in Dogs. Anesthesiology *22*: 139 (1961).
5. Bamforth, Betty J., Siebecker, Karl L. *et al.* Effect of Epinephrine on the Dog Heart during Methoxyflurane Anesthesia. Anesthesiology *22*: 169 (1961).
6. Stephen, R. C. Personal Communication.