CLINICAL EXPERIENCE WITH METHOXYFLURANE (PENTHRANE®)

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METHOXYFLURANE (Penthrane—Abbott) is the most recent of the inhalational anaesthetics. It is a fluorinated ethyl methyl ether of low toxicity and has a characteristic sweet odour. Boiling point is 104.8° C., vapour pressure is 25 mm. Hg at 20° C., and the oil/water distribution coefficient is 400. It is therefore a drug of low volatility and highly soluble in fat. These properties account for the slow uptake and slow elimination of methoxyflurane from the body.

The vapour pressure and efficiency of the vaporizer limit its concentration to a maximum of 4 per cent.¹ It is non-inflammable and non-explosive in air or oxygen under conditions prevailing in an operating room.

Five hundred surgical cases anaesthetized with methoxyflurane are classified in Table I and represent a reasonable cross-section of the work done in a small general hospital. The age range was from six months to ninety-four years. There were 79 children, 276 adult females, and 145 adult males.

TABLE I
500 CASES WITH METHOXYFLURANE

Operation	No. of cases
Thoracic	5
Upper abdominal	62
Lower abdominal	72
Orthopaedic	46
Urological	25
Plastic	28
Anus and rectum	49
Extremities	34
Hernia	46
Tonsils and adenoids	70
Perineal	63
	500

Methoxyflurane was used in the ether bottle of a Boyle's machine, and in 4 per cent and 10 per cent Fluotec vaporizers. Administration with all three was satisfactory, although the 4 per cent vaporizer was used only in the very young and very old.

Tables II and III show the results of calibrating the ether bottle and 10 per cent Fluotec for methoxyflurane. The percentages shown in Table III are somewhat less than those reported by McIntyre and Gain,² but the accuracy of vaporization with ether bottles is such that each machine would probably show considerable variation.

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TABLE II
CONCENTRATIONS WITH 10 PER CENT FLUOTEC
VAPORIZER

% Fluotec	Max., %	Min., %
4	0.5	0.43
5	0.55	0.5
6	0.62	0.58
7	0.83	0.76
8	1.12	0.97
9	1.25	1.04
10	1.4	1.25

TABLE III
CONCENTRATIONS WITH ETHER BOTTLE, BOYLE'S MACHINE, AND
LEVER ON FULLY

	Max., %	Min., %
Plunger down fully (bubbling)	2.6	2.43
Plunger at liquid level	1.5	1
Plunger half raised	0.97	0.8
Plunger fully raised	0.78	0.6

The concentrations with the 10 per cent Fluotec were higher than expected at the 8, 9, and 10 per cent openings, which may possibly be due to original faulty calibration. This demonstrates the value of measuring the concentrations for each piece of apparatus.

The maximum concentration delivered by the 10 per cent Fluotec was inadequate to settle the patient in a few instances, and it was then supplemented by methoxyflurane from the ether bottle. When inductions were carried out with nitrous oxide - oxygen and methoxyflurane, the ether bottle was found to be more satisfactory owing to the higher concentration available.

The lower openings on the 10 per cent Fluotec were useful for more accurate delivery of low concentrations for maintenance and gradual withdrawal of the anaesthetic.

TECHNIQUES

Induction with nitrous oxide - oxygen and methoxyflurane is smooth and without excitement, but prolonged, and in most instances impractical. Gradual introduction of the drug is essential to avoid coughing. On an average it took 11 minutes to reach surgical anaesthesia and 17 minutes for sufficient depth to intubate without reaction.

The most satisfactory method of induction is the thiopental-succinylcholine-methoxyflurane sequence when intubation is to be performed. Initial difficulty was experienced with bucking on the endotracheal tube after the effects of the succinylcholine had worn off. The volatility of methoxyflurane being low, control of the patient was difficult in these circumstances. The technique now adopted is to ventilate the patient with approximately 1 per cent methoxyflurane before the return of muscle tone. This invariably gives smooth anaesthesia. Adequate

topical anaesthesia of the larynx will also obviate this complication, as will small doses of thiopental (50 mg.) or meperidine (10 mg.).

TECHNIQUE FOR ADENOTONSILLECTOMY

Methoxyflurane was found to be very satisfactory for tonsillectomy and adenoidectomy in children. It must be emphasized that care and patience are necessary to produce good results. Premedication is as follows:

Children over 50 lb.	Atropine 0.4 mg. Meperidine 0.5 mg./lb.
Children under 50 lb.	Atropine 0.3–0.4 mg. Meperidine 0.5 mg./lb.
OR	
	Atropine 0.3–0.4 mg. Promethazine 0.5 mg./lb.

THEN

Rectal thiopental in O.R. 12 mg./lb.

The group over 50 lb. were given intravenous thiopental¹⁰ 2½ mg./lb. followed by succinylcholine 30–40 mg., and then intubated.

The children under 50 lb. who had received basal narcosis with rectal thiopental were induced with nitrous oxide–oxygen and cyclopropane, or halothane. They then received succinylcholine, 20 mg. approximately, and were intubated. Anaesthesia was maintained in both groups with nitrous oxide–oxygen (4:4) and methoxyflurane, using a Stephen-Slater valve or "T" piece, the latter for the small children.

After intubation the child was gently ventilated with 0.5–1 per cent methoxyflurane. With the return of spontaneous respiration, 1–1.5 per cent methoxyflurane was given for 5–7 minutes before permitting the surgeon to commence. If there was no reaction when the first tonsil was grasped, the methoxyflurane was reduced to 0.5 per cent and discontinued after both tonsils had been removed. At the completion of the procedure, the child was usually swallowing and moving.

CHARACTERISTICS OF METHOXYFLURANE ANAESTHESIA

Induction is slow but tranquil. Analgesia appears early and is a valuable property of this agent.³ Salivation and bronchial secretions are absent; relaxation is good in surgical anaesthesia, and cadaveric in the deeper planes. Respirations are depressed from surgical anaesthesia on, and the minute volume is greatly reduced when measured with a ventilation meter. The pulse is stable and in only three instances was a bradycardia detected.

Blood pressure falls a little and is a useful gauge of anaesthetic depth. Hypotension may be encountered in the following instances:

1. In deep anaesthesia.
2. During controlled ventilation.
3. In the geriatric patient.

Hypotension can be profound in deep anaesthesia and a vasopressor may be necessary, while anaesthesia is being lightened.

With controlled ventilation hypotension is sometimes seen even in the lighter planes of anaesthesia and blood pressure recordings should be checked frequently.

The geriatric patient is prone to steep falls in blood pressure unless very light anaesthesia is used. Any attempt to increase the depth results in hypotension, especially in the hypertensive patient.

Figure 1 is the anaesthetic record of a 94-year-old lady for hip pinning. She was in reasonable physical condition for her age, and weighed 150 lb. The figures along the bottom line represent the settings on the 4 per cent Fluotec

FIGURE 1.

vaporizer. She was induced with Brietal® 50 mg. and 30 mg. of succinylcholine. She reacted to the endotracheal tube and was given a further 10 mg. of Brietal.® Anaesthesia was without further incident except for the hypotension, and this occurred despite the low concentration of methoxyflurane used. Blood loss was considerable and 1000 ml. was replaced. It is quite probable that she was hypovolaemic to begin with; nevertheless, it is felt that in geriatric patients hypotension is the rule with methoxyflurane unless minimal concentrations are employed, and sometimes despite this precaution.

RELAXANTS AND METHOXYFLURANE

All the relaxants used were compatible with methoxyflurane, i.e., gallamine, *d*-tubocurarine, and succinylcholine chloride. It was a distinct clinical impression that the non-depolarizing group were potentiated by methoxyflurane.

TABLE IV

Case No. and sex	Age	Wt.	Time, hours	Operation	Muscle relaxant	Nausea and/or vomiting	Interval before post-op. analgesic, hours	Complications
1.F.	34	141	2	Ovarian tumour	Gallamine 30 mg.	No	6	Nil
2.F.	42	163	1	Abdominal wound dehiscence	Gallamine 50 mg.	No	8	Cough with expectoration
3.F.	67	154	1 25	Cholecystectomy	Gallamine 40 mg.	No	2	Basal pneumonia
4.F.	68	173	4 25	Resection of sigmoid and hysterectomy	Gallamine 100 mg.	No	No postop. analgesic drugs	Nil
5.F.	32	109	1 5	Cholecystectomy	Nil	Yes	5	Nil
6.F.	51	111	2 5	Hysterectomy	Gallamine 80 mg.	No	7.25	Nil
7.F.	45	138	1 5	Cholecystectomy	Nil	Yes	4.25	Headache
8.M.	62	130	4	Gastric resection	Gallamine 100 mg.	No	11	Cough with expectoration
9.F.	73	152	1 5	Left lumbar sympathectomy	Gallamine 20 mg.	Yes	3	Nil
10.F.	49	123	2	Ovarian cyst	d-Tubocurarine 3 mg.	Yes	4	Nil
11.F.	40	96	2	Vagotomy and gastroenterostomy	Gallamine 40 mg.	No	5 5	Nil
12.M.	52	184	1 5	Cholecystectomy	Gallamine 80 mg.	No	9.25	Nil

The details of 12 consecutive unselected intra-abdominal procedures are shown in Table IV. It will be immediately apparent that the dose of relaxant used was far less than with other anaesthetic drugs. All 12 cases received intubating doses of succinylcholine.

As a consequence of the small amounts of relaxants used, spontaneous respiration was adequate when allowed to return, and anticholinesterase drugs were unnecessary except in one instance. This was in case No. 12, where it was felt that a little curarization remained and 10 mg. of edrophonium was given in the recovery room.

The absence of postoperative respiratory difficulties was gratifying, particularly in the obese patients. These sometimes require large doses of relaxant drugs, which can be difficult to reverse postoperatively. It is now felt that methoxyflurane anaesthesia with minimal relaxants is the anaesthetic "par excellence" for these people for intra-abdominal surgery. The distressing postoperative respiratory inadequacy often seen in these patients can be obviated by the use of balanced anaesthesia with methoxyflurane.

None of the respiratory complications were of a serious nature, and they were present before operation in case No. 2. The prolonged nature of the surgical procedure in case No. 8, plus the presence of a smoker's cough preoperatively, probably contributed to the respiratory morbidity. The right basal pneumonitis developed in case No. 3 despite pre- and post-operative I.P.P.B. with bronchodilator and mucolytic agents. She was a short, obese lady who was expected to develop a "chest."

TABLE V
RESULTS IN 500 CASES OF METHOXYFLURANE

Recovery time	15-90 minutes
Patients not requiring analgesics	8.2%
Nausea	10.9%
Vomiting	8.6%
Headache	2.8%
Pulmonary complications	6.8%

RECOVERY TIME

Prolonged recovery was the rule for the first 100 cases. Increasing experience reduced this considerably, first by a reduction in the maintenance dose to 0.3-0.5 per cent, and secondly by the discontinuing of methoxyflurane 15-25 minutes before the end of the surgical procedure. With adequate experience it is possible to have most patients responding before they leave the operating room.

The post-tonsillectomy paediatric patients were fully recovered in 15-20 minutes. Restlessness was less than with halothane, 1 in 5 requiring sedation as against 1 in 3 with the latter drug.

POSTOPERATIVE ANALGESIA

This was neither a dependable nor a consistent occurrence. When analgesia does occur it can be extremely useful in obviating the need for analgesic drugs, thus lessening the risk of respiratory depression and complications.

Apart from the 8.2 per cent who did not require analgesics, there were many other patients who experienced postoperative analgesia for up to 21 hours. The longer the surgical procedure, the more was analgesia experienced postoperatively. Long orthopaedic operations, in particular, appeared to have analgesia, more often than other cases.

Even in the absence of pain relief, restlessness was not a feature of recovery.

NAUSEA AND VOMITING

The figures given are for the first 12 hours postoperatively and are exclusive of the 70 tonsillectomy and adenoidectomy cases. A high incidence was experienced in patients in whom methoxyflurane was used for muscular relaxation without relaxant drugs; consequently deep anaesthesia must be blamed.

HEADACHE

This occurred in 11 females and 3 males. No adequate explanation is offered for this. As ten of the headaches occurred in the first 120 anaesthetics it may be that coughing on the endotracheal tube was the cause.

It is possible that methoxyflurane can cause headache *per se* as some of the nursing staff complained of this when it was first introduced.

PULMONARY COMPLICATIONS

Again the 70 tonsillectomy and adenoidectomy cases were excluded from this group. Bronchitis was the commonest type of complication. I.P.P.B. was freely used both in pre- and post-operatively in suspect cases and may have helped to keep the incidence low. Undoubtedly some mild "chests" were missed, but the number cannot have been large.

METHOXYFLURANE AND EPINEPHRINE

Seven adults and one child were given methoxyflurane when epinephrine was used by the surgeon. None of the adults gave any cause for anxiety. Five were monitored with a cardioscope and no abnormal rhythms were detected.

The child was 4½ years old, and weighed 42 pounds. A partial S.M.R. was performed and a solution containing 1/100,000 epinephrine was injected into the septum. The operation took 20 minutes, but at the end of that period the pulse rate had risen to 180 per minute. The concomitant use of these drugs in smaller children should therefore be applied with caution.

DISCUSSION

Methoxyflurane is a satisfactory anaesthetic agent, with many useful properties.

Used as the analgesic and relaxant in balanced anaesthesia, it is suitable for intra-abdominal surgery. It is preferable, however, to use minimal doses of relaxant drugs to avoid the necessity for deep anaesthesia and prolonged recovery.⁴ Anticholinesterase drugs are seldom necessary to reverse the small doses of relaxants.

Because of the high fat solubility, with its slow release into the blood stream, methoxyflurane is potentially an agent from which recovery will be slow.⁵ This

need not necessarily be a disadvantage and can obviate the need for postoperative sedation for some hours.

Power's⁶ figures for nausea and vomiting were 20 per cent and 10 per cent respectively, which are higher than in this series. Others have described the incidence of these complications as minimal.^{5,7} Comparative figures for nausea and vomiting using some of the other anaesthetic agents are 40.6 per cent,⁸ 41 per cent,⁹ 15.5 per cent.¹⁰ Belleville¹¹ had an incidence of 26 per cent using cyclopropane and of 16.5 per cent using ether. It would appear, therefore, that in this respect methoxyflurane comes somewhere between ether and cyclopropane in this series.

In the tonsillectomy and adenoidectomy group extubation laryngospasm was remarkably absent. This has been commented upon by two other authors.^{12,13} Relief from this distressing complication is much to be desired, as a brief period of laryngospasm with consequent anoxia can cause postoperative restlessness and delirium.

No clinical contraindications to methoxyflurane were found, with the possible exception of its use with epinephrine in children. As it was used in only one such case, no definite opinion can be formed. In a recent series of 150 cases where methoxyflurane and epinephrine were used¹⁴ the effects on the heart and circulation were transient. It was not stated that any children were included in the group.

Cardiac rate, rhythm, and blood pressure are stable under methoxyflurane anaesthesia.^{12,7} Three instances have been mentioned in which hypotension may occur. Methoxyflurane is therefore a potential hypotensive agent, but there is less danger of this with it than with halothane. In dogs, cardiac output fell with halothane to a greater degree than with methoxyflurane.¹⁴ This is exemplified by two patients in this series who had received Dibenzyline® preoperatively for ganglionic blockade. Their blood pressures were 90 mm. and 100 mm. Hg on arrival in the operating room. In both, the hypotension was aggravated by halothane and a change to methoxyflurane restored both to the preoperative levels.

Control of respiration is greatly facilitated by the use of methoxyflurane, particularly if an automatic ventilator is used.¹² During surgical anaesthesia there is reduction in respiratory minute volume⁵ and respirations should be assisted or controlled. Wyant⁴ found that a sharp drop in pH and a rise in pCO₂ occurred on spontaneous respiration with a slight recovery during controlled respiration.

Hepatic toxicity has been described as similar to that with halothane,¹⁶ and also ether.^{7,12} In this series no evidence of hepatic dysfunction was found. Some of the patients had liver disease preoperatively, which was not intensified by the anaesthesia, and all recovered satisfactorily.

SUMMARY

A series of 500 cases anaesthetized with methoxyflurane is presented.

It was found to be a useful agent in intra-abdominal surgery, particularly in the obese. The dosage of relaxant drugs could be considerably reduced, so that respiratory inadequacy postoperatively was minimized. Anticholinesterases were seldom necessary.

Postoperative respiratory complications were rare, and the incidence of nausea and vomiting was considered somewhat between that of ether and that of cyclopropane.

Postoperative analgesia was unpredictable, but valuable when it did occur.

In 70 tonsillectomy and adenoidectomy cases, restlessness was significantly diminished postoperatively. Care and patience are prerequisites for good results in these cases.

Muscular relaxation, peroperative analgesia, non-explosiveness, and probable compatibility with epinephrine are valuable properties of this drug. Doubt is expressed as to the compatibility of methoxyflurane and epinephrine in children.

Although cardiac rate, rhythm, and blood pressure are usually stable, methoxyflurane is a potential hypotensive (*a*) in deep anaesthesia, (*b*) in geriatric patients, and (*c*) during controlled ventilation.

RÉSUMÉ

Nous présentons une série de cas d'anesthésie au méthoxyflurane.

Nous avons trouvé qu'il était un agent utile en chirurgie abdominale, surtout chez les obèses. La quantité de myorésolutifs requise est beaucoup moindre, de sorte que l'hypoventilation postopératoire est très réduite. Rarement nous avons dû recourir à l'usage d'anticholinestérasiques.

Les complications pulmonaires postopératoires ont été rares et la fréquence des nausées et des vomissements se situe entre celle de l'éther et celle du cyclopropane.

L'analgesie postopératoire était imprévisible, mais appréciable si elle était présente.

Chez 70 malades opérés pour amygdalectomie, adénoïdectomie, nous avons noté une diminution marquée de l'agitation postopératoire. Dans ces cas-là, pour obtenir de bons résultats, il faut de la patience et du dévouement.

Les précieuses propriétés de cet agent sont: le relâchement musculaire, l'analgesie peropératoire, l'inexplosivité et la compatibilité probable avec l'épinéphrine. Cependant, chez les enfants, il persiste un doute sur la compatibilité du méthoxyflurane avec l'épinéphrine.

Ordinairement, au cours de l'anesthésie au méthoxyflurane, la vitesse et la régularité du pouls ainsi que la tension artérielle sont stables; cependant, cet agent demeure un hypotenseur en puissance (*a*) si l'anesthésie est profonde, (*b*) chez les vieillards, et (*c*) si l'on contrôle la ventilation.

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