METHOXYFLURANE* — A NEW ANESTHETIC AGENT

A Clinical Evaluation Based on 206 Cases

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METHOXYFLURANE, the most satisfactory anesthetic agent of a series of fluorinated hydrocarbons and fluorether studied clinically by Artusio and Van Poznak,[1] was used by us to induce or to maintain anesthesia in 206 patients. This anesthetic agent is a nonexplosive liquid that produces profound analgesia accompanied by remarkable muscular relaxation with apparently low toxicity. In low vapor concentrations, methoxyflurane produces the same degree of analgesia produced by halothane, the same degree of muscular relaxation produced by deep levels of cyclopropane anesthesia, and possesses the same wide margin of safety as that of diethyl ether.

Introduced experimentally as DA-759, methoxyflurane is 1,1-dichloro-2, 2-difluoro-2-methoxyethane. The chemical structure is shown in *Figure 1.* It is a

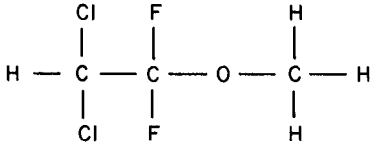

Fig. 1. Structural formula for methoxyflurane.

clear, colorless liquid that boils at 104.8 C. (220 F.) ± 0.2 degrees at 760 mm. of Hg, and has a specific gravity of 1.4224. The odor is pleasant with a fruity characteristic. The explosive range is shown in *Table 1.* At 20 C. (68 F.) the explosive limits in air and oxygen are zero. The flash point is 56.11 C. (133 F.). The vapor density at 37 C. (98.6 F.) is 7.36 gm. per liter. It is miscible in all proportions with olive oil (liquid to liquid). Its solubility in water, according to polarographic titration is 0.22 gm. per liter of water.

The olive oil/water distribution coefficient was determined for 1 per cent methoxyflurane as 400. Using a 10 per cent concentration of methoxyflurane, the distribution constant was 39. Diethyl ether is 3.8 and halothane is 330. *Table 2* lists the vapor pressures of methoxyflurane.

The absolute viscosity at 20 C. is 1.070 and at 50 C. is 0.703 centipoise. The surface tension at 20 C. is 25.55 and at 50 C. is 22.61 dynes per centimeter. The

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Table 1.—*Explosive range of methoxyflurane*

Methoxyflurane mixed with	Percentage, per cent	Temperature C.	Temperature F.	Percentage, per cent	Temperature C.	Temperature F.
Air	9	80	176	28	105	221
Oxygen	4	60	140	28	105	221

Table 2.—*Vapor pressures of methoxyflurane*

Pressure, mm. of Hg	Temperature, C.
665.06	100.15
558.94	94.78
459.78	88.78
188.93	64.52
90.29	47.24
40.0	29.0*
30.0	24.4*
10.0	5.0*

*Extrapolated value.

ultraviolet-absorption spectra and infrared-absorption spectra of methoxyflurane were studied by Chenoweth.[2]

With the Vernitrol (Heidbrink) vaporizer the amount of methoxyflurane vaporized was measured during various flow rates of 100 to 1000 ml. through the vaporizer. The temperature of the vaporizer was 23 C. (74 F.) for all the determinations. Each determination was made by replacing the measured volume of methoxyflurane; 1 ml. of liquid forms 209.7 of vapor.

Table 3 shows the percentages of vaporization with the various flow rates. Because the temperature of liquid methoxyflurane in the vaporizer remained constant at the higher flow rates, at 23 C. an average of 3.7 per cent methoxyflurane vapor resulted from 26 ml. of oxygen in the vaporizer and 1 ml. of methoxyflurane. By extrapolation, the vapor pressure of methoxyflurane (for 30 minutes at 24 C. and 28 ml. of oxygen flow through the vaporizer) is 1 ml. of methoxyflurane vapor for a vapor percentage of 3.57 per cent. Thus, our percentage of vaporization, according to average determinants is close to the theoretic value.

The percentage of methoxyflurane vaporized with a Heidbrink ether wick vaporizer was determined for a 4-liter flow at various openings of the vaporizer.

Table 3.—*Vaporization of methoxyflurane at 23 C. in the Heidbrink No. 8 wick vaporizer*

	Flow rate, milliliters per minute		Percentage of methoxyflurane vapor, per cent
	Vaporizer oxygen	Methoxyflurane vapor	
	100	3.78	3.78
	200	10.5	5.25
	300	9.8	3.26
	400	18.2	4.37
	500	18.2	3.52
	600	22.4	3.63
	700	24.5	3.38
	800	30.8	3.71
	900	35.0	3.75
	1000	38.5	3.72
Average	26 ml.	1 ml.	3.7 per cent

This was done by measuring the amount of liquid methoxyflurane vaporized in one hour, and calculating the percentage of vapor on the basis, as previously stated, that 1 ml. of liquid methoxyflurane vaporizes into 209.7 ml. at 23 C. The temperature of the liquid methoxyflurane in the vaporizer varied one degree, from 22 to 23 C. *Figure 2* shows the percentages of methoxyflurane vaporized at various openings of the vaporizer with a 4-liter flow of oxygen.

Metabolic Effects

Since the publication of reports of fatal hepatic damage following chloroform anesthesia, each new substance introduced as a possible anesthetic agent has been evaluated for potential toxic effects on the vital organs and tissues of the body as well as for efficiency in producing anesthesia. It is well established that the members of this group of halogenated hydrocarbons have great potential toxic properties, particularly for the liver. Of the numerous biochemical assays of hepatic function, we used four basic tests on our patients: the tests for blood sugar, Bromsulphalein retention, serum alkaline phosphatase, and serum bilirubin.

Blood sugar assays were made preoperatively to provide a base line in each case, and two additional assays were made during anesthesia, one shortly after induction, the other at the end of the administration of methoxyflurane. The tests were repeated 24 hours postoperatively and at intervals thereafter until the patient was discharged from the hospital.

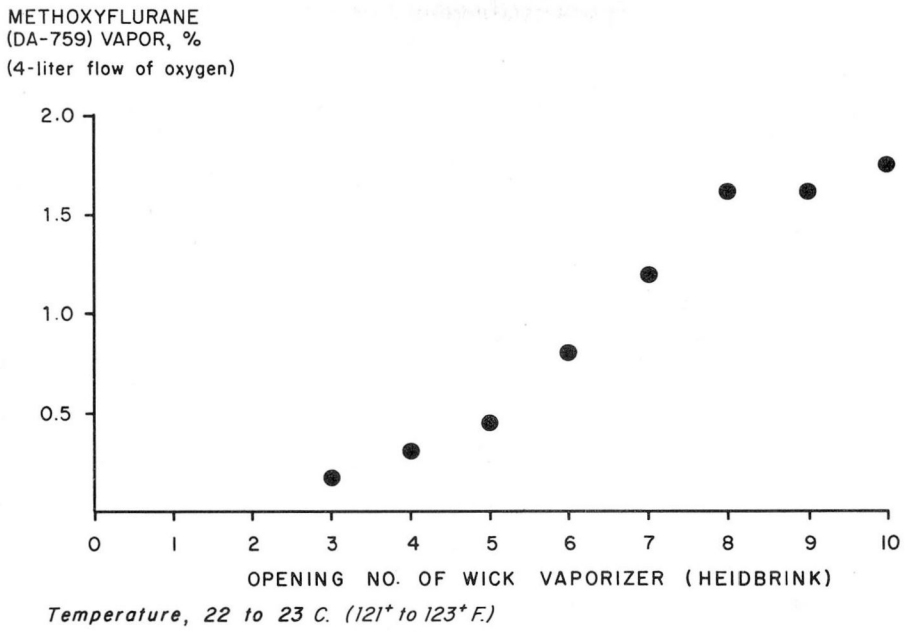

Fig. 2. Chart showing percentages of vaporization of methoxyflurane.

The most striking effect of methoxyflurane was on the blood sugar concentrations. Following induction of anesthesia with methoxyflurane there was a significant rise in the concentration of blood sugar, generally of the order of 10 to 20 mg. per 100 ml. This rise was maintained during the course of anesthesia. *Table 4* shows the values obtained in six patients. The hyperglycemia did not persist postoperatively, despite the fact that all the patients received 5 per cent dextrose intravenously in the immediately and the late postoperative periods. The

Table 4.—*Rise of blood sugar in six patients receiving methoxyflurane anesthesia*

Patient no.	Blood sugar, mg. per 100 ml.			Percentage rise, per cent
	Preoperative	Postinduction	At conclusion of operation	
1	81	95	138	72
2	75	90	118	60
3	70	97	111	57
4	80	93	—	—
5	66	84	92	39
6	72	84	80	11

mode of action of the drug in producing the rise in concentration of blood sugar is presumed to be similar to that described for ether. It is improbable that hypoxia plays a part in this hyperglycemia but, as in the case of agents previously studied, increases in endogenous blood epinephrine, depression of enzymatic activity, blood loss, and sympathetic stimulation cannot be excluded from consideration as factors contributing to this rise.

To date, the small number of patients who have been followed precludes final conclusions as to the effect of methoxyflurane on hepatic function, but the initial impressions seem to be that the impairment of function is comparable to that produced by ether, and that hepatic glycogenolysis with hyperglycemia takes place during anesthesia from methoxyflurane. All patients showed increased retention of the Bromsulphalein in the first 24 hours postoperatively, and gradual return to preoperative values within four or five days.

The alkaline phosphatase and serum bilirubin values were little altered. One patient, a 57-year-old man, however, showed definite alterations in the postoperative values. He was a known alcoholic who had an acute alcoholic exacerbation in the recent past, and it is possible that similar hepatic alterations would have occurred with any other inhalant.

Technic of Administration

Methoxyflurane may be administered in the two ways diethyl ether is administered, by: open-drop technic, or vaporization in a Heidbrink No. 8 wick vaporizer. We used the semiclosed and closed technics. In most instances intubation was employed after using the thiopental sodium—succinylcholine—oxygen sequence. The volume flow of oxygen was usually set at 4 liters, and the vaporizer opening at No. 1 was quickly turned to Nos. 5 or 6. At that flow rate, the patient rapidly became relaxed and anesthetic.

One is immediately impressed with the great amount of muscular relaxation that occurs. Frequently it was sufficient for the entire surgical procedure. But, inasmuch as the amount of relaxation varies with the duration and type of the operation, additional relaxant agents may be required. For example, a great amount of relaxation was needed for procedures such as vagotomy and high resections of the splenic flexure.

Methoxyflurane was administered to induce anesthesia in a few patients. The inhalation of methoxyflurane vapor was somewhat irritating, and the patient coughed during induction of anesthesia. As there were no clinical signs to indicate the level of anesthesia, the stages of anesthesia are difficult to outline. The induction was fairly long, similar to induction of diethyl ether. The excitement stage was short and often was absent. However, the stage of analgesia occurred with exceeding rapidity, especially in the women in labor. Inhaling of the vapor at the time of each successive pain produced a cumulative effect: soon the patient

not only was analgesic but lost consciousness, and the forward progress of the infant's head against the perineum ceased to be painful. However, the analgesia was not equal to the anesthesia necessary to perform surgical procedures, and with application of the forceps, additional amounts of anesthetic agent were required.

The status of the blood pressure is one criterion for judging levels of anesthesia. With deep levels, a fall in blood pressure was noted in many patients, on occasion to 80 mm. of Hg. The hypotension occurred most often when a deeper level of anesthesia was used to obtain additional relaxation. By lightening the anesthesia the hypotension was reversed. Some anesthesiologists contend that additional doses of atropine sulfate will correct this low systolic pressure.

The respiratory pattern in most instances was not altered either in rate or in depth. However, when an automatic respirator was employed, the patient's respirations were easily controlled. When anesthesia was deepened beyond surgical requirements, there were no aberrations in cardiac rhythm or respiratory pattern.

The patient's recovery period, too, was extremely long, as would be expected from the physical characteristics of the anesthetic agent. It was necessary to stop administering the vapor at least from one-half to one hour before the operation was completed. When the vapor was not discontinued in time, the patient did not arouse until the remotely postoperative period. This delay encouraged postanesthetic atelectasis in some of our first patients treated. However, after methoxyflurane anesthesia, a period of analgesia persisted for an extended time into the postanesthetic period. During this time the patient was awake or was easily aroused and was in possession of his vital reflexes.

Postanesthetic Emergence

During the recovery period the patient passes through a phase of regaining his vital reflexes (emergence), followed by the return of his higher reflexes and functions (arousal). Clearly the duration and technic of anesthesia, the nature of the surgical procedure, and the condition of the patient will all play their parts in influencing the results obtained in evaluating an inhalation agent from this point of view. With due regard to these factors, 35 patients were studied by personal observation in the period of emergence, arousal, and the immediately postoperative period.

According to the duration of anesthesia, and the technic employed, the time for emergence ranged from 10 minutes to one and one-half hours. Toward the end of the series, most patients returned from surgery in full possession of their vital reflexes. The period of arousal, which was gauged from the time the patient moved in response to commands or stimuli to the point at which he was fully rational and orientated in time and space, was often prolonged. After physical stimulation or questioning, the patient might lapse into sleep. The average time for full arousal was from one to two hours, and even then, there was a tendency to somnolence in many patients.

The appearance of the patient. The most striking feature to be observed in these patients as they entered the recovery room, was the chalky whiteness of their skin. This applied to all patients except those with pre-existing hyperpigmentation of the skin. The pale skin, however, was warm and dry, with the exception of the fingers and toes of some patients, which were cold and exhibited some peripheral cyanosis of the nail beds. The chalky pallor of the warm dry skin persisted into the period of arousal, being least obvious when the patient was fully awake and alert.

Eye reflexes and movements. The light reflex and consensual reaction were active in all patients who returned from surgery. In those who had not negotiated the stage of emergence the pupil was fixed in the central position. The conjunctival and corneal reflexes were not investigated in order to avoid trauma to the surface of the eye. Lacrimation and return of activity of the lid and eyelash reflexes usually coincided with each other and with the return of eyeball movements. Normal activity of the eye reflex and normal eye movements were not apparent until the swallowing and laryngeal reflexes were active. There were no nystagmus, difficulty with accommodation, or inflammation of the conjunctivae apparent in these patients in the postoperative period.

Vital reflexes. In all patients returned to the recovery room with an endotracheal tube still in situ, because the vital reflexes had not returned, coughing could be evoked by stimulating the carina or trachea with a catheter passed down the endotracheal tube, or by moving the endotracheal tube and irritating the walls of the larynx and trachea. However "spontaneous" coughing did not occur even after the vital reflexes had returned. The laryngeal reflex became active as soon as swallowing and gagging were observed, and after this, eye movements became active.

At the beginning of the series, two patients retained their endotracheal tubes for one hour and one and one-half hours. This emergence was partly due to the duration of the operation, and partly to the technic of administration.

On extubation there was no incidence of laryngospasm in any patient, and mucous secretion was moderate in amount. However there is no inhalation technic in which laryngospasm is unknown, and the use of methoxyflurane will probably prove to be no exception as the series enlarges.

In those patients with an oropharyngeal airway inserted it was found that a gag reflex could be excited by moving the airway about in the mouth, but if left undisturbed the patient retained the airway until emergence was complete. The patient would often reach up and remove the airway himself and then lapse back into sleep. Vomiting and regurgitation did not occur during emergence, but three patients were nauseated and vomited after the return of their vital reflexes.

Patients completed their emergence, therefore, without laryngospasm, coughing, or vomiting, and without evidence of excessive excitement or delirium. No doubt these features will be encountered as more cases are investigated, but it is believed

that the incidence will be lower than with, for example, diethyl ether.

Seven patients had bouts of shivering and shaking of the extremities. These ranged from fine vibrations of the lower jaw and forearms to extravagant jerking movements of the head and limbs, sufficient to shake the bed in one instance.

The stability of the cardiovascular system. As gauged by measurements of the pulse rate and systemic blood pressure at 15-minute intervals until leaving the recovery room, all these patients demonstrated a remarkable cardiovascular stability. Most patients retained their preoperative pulse rates and systemic blood pressure levels, and in those patients returned from surgery with blood pressures below their normal limits, there was no further deterioration.

The adequacy of respiration. Measurements were made of the minute volume and respiratory rate of patients who were sufficiently anesthetized to retain their endotracheal tubes. In all instances an adequate tidal volume for the patient was evident.

As these postoperative patients appeared free from pain, it was necessary to administer an analgesic drug to only seven patients. Although this was advantageous in some respects, it removed all stimulus for movement and encouraged the accumulation of mucous secretions at the lung bases. These patients were deeply asleep. In the more remotely postoperative period, few complications were noted. However, early in the study, there was evidence of pulmonary atelectasis in six patients. One minor inconvenience when methoxyflurane was used as the sole agent was the persistent characteristic odor of the substance in their rooms and about their persons on the day following operation.

It is apparent that in those patients in whom methoxyflurane was used as the sole agent for procedures requiring anesthesia for more than a half hour, emergence was safe, but full arousal was undoubtedly prolonged.

Discussion

Since the concept of balanced anesthesia was introduced, and the discovery of the ultra-fast-acting barbiturates, the skeletal muscle relaxants, and a series of analgesic drugs for intravenous use, intravenous anesthesia has received an impetus with which few inhalation agents have been able to compete.

The search for the perfect inhalation agent has been relentlessly pursued, because, if such an agent were found, all the requirements of perfect general anesthesia could be displayed in a spontaneously breathing patient who could be detoxicated at will, simply by ceasing to administer the inhalation agent. This would be most desirable in prolonged procedures, when the polypharmacy of the intravenous technics is evident as its greatest disadvantage. The fact that respiration must invariably be assisted or controlled with intravenous methods is also undesirable in prolonged procedures.

It is also worth noting that, owing to the multiplicity of electric equipment often required in the modern operating room, any new agent must fulfill the addi-

tional requirement of being nonexplosive. Another unwelcome criterion to be fulfilled by any new agent is the requirement for compatibility with a variety of new chemicals that may have been administered to the patient before or during anesthesia. The incompatibility of diethyl ether with tetraethylthiuram disulfide, and of halothane with ataractics, ganglion-blocking agents, vasopressors, and relaxants, afford examples. It is against this background of problems that any new inhalation agent must be evaluated, and so much more is expected of such drugs now, than was ever hoped for in the past, that of the numerous chemical compounds evaluated in the last 10 years only one, halothane, has qualified for use.

Under the prevailing conditions it would appear that methoxyflurane, which is a nonexplosive inhalation agent is suitable as a supplementary agent to provide analgesia and muscle relaxation mainly in prolonged abdominal surgery. One may reflect that if methoxyflurane had been discovered at the time when ether and chloroform were newly in use, it might have superseded them both and become a byword in anesthesia, but this is hardly likely to occur today.

In the light of our findings it seems that, under the conditions of administration so far investigated, there is a definite but limited place for the use of methoxyflurane as a supplementary agent to provide additional analgesia. When so used with nitrous oxide it achieves some muscle relaxation and thereby reduces the amount of neuromuscular blocking agents required. The fact that it is nonexplosive, and does not react with soda-lime, enables it to be used safely under circumstances when other agents such as cyclopropane or trichlorethylene would be dangerous. Induction was most easily accomplished with a thiopental sodium—succinylcholine—oxygen sequence. It was not always easy to decide whether the patient was at a plane of anesthesia suitable for surgical stimulation. Except for central fixation of the eyeball, the ocular signs, so useful in the diethyl ether anesthesia, were not in evidence. A reliable criterion was the patient's ability to tolerate an airway or endotracheal tube, the onset of muscular relaxation, and the lack of reflex response to painful stimulation.

When used as a supplement to achieve balanced anesthesia, arousal was not delayed. Particularly satisfactory anesthesia was evidenced when methoxyflurane supplemented the thiopental sodium—nitrous oxide—oxygen sequence. Sometimes the addition of muscle relaxants will be necessary with this technic.

When used as the primary agent with air or oxygen, methoxyflurane has little to commend it. The prolonged somnolence outweighs the advantages of prolonged analgesia. We believe, therefore, that, except in infants, who appear to be suitable for induction with this agent, induction by inhalation of methoxyflurane is marred by the long time required, and by the difficulty to judge when it is complete. However, induction was free from the side effect of vomiting, and, although inducting was not so smooth as that with halothane or cyclopropane it was easier than with diethyl ether.

Probably methoxyflurane will find its widest application in abdominal surgery

and gynecologic procedures *(Table 5),* and possibly in neurosurgery and ophthalmic operations. It may prove suitable for general anesthesia in obstetrics, but this use has not yet been thoroughly investigated. It probably has a wide mar-

Table 5.—*Procedures or operative areas in 206 patients receiving methoxyflurane anesthesia*

Procedure or area	No. of patients
Abdominal	74
Gynecologic	32
Arteriography	26
Perineal	20
Head and neck	14
Thoracic	13
Genitourinary	9
Extremities	7
Other	6
Neurosurgical	5
Total	206

gin of safety, but we cannot assume this when it has been in use for such a short time. It should be remembered that chloroform was used for many years before the first fatality was reported, and it was even many years later that it acquired a perhaps undeservedly bad reputation.

Summary

A new nonexplosive inhalation agent, methoxyflurane (DA-759), has undergone clinical trial in 206 patients, following a preliminary trial by others in 300 patients. It appears to be a useful supplementary inhalation agent, and its properties, clinical characteristics, possible uses and value are discussed, but time alone can determine its place in modern anesthetic practice.

References

1. Artusio, J., and Van Poznak, A.: Personal communication.

2. Chenoweth, M.: Personal communication.