# A CLINICAL EVALUATION OF METHOXYFLURANE IN MAN

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ROBBINS in 1940 [1] studied a large series of fluorinated hydrocarbons; however, none of these agents was tested in man. In 1953 Krantz, Carr, and Bell [2] introduced trifluoroethyl vinyl ether (Fluoromar), and in 1956, Raventós [3] and Suckling [4] introduced 2-bromo-2-chloro-1,1,1-trifluoroethane (Fluothane) as a clinically useful anesthetic. Beginning in 1956, Van Poznak and Artusio investigated a series of fluorinated hydrocarbons and fluorinated ethers in the dogs.[5, 6, 7] Based upon its performance in the dog, the compound 2,2-dichloro-1,1-difluoroethyl methyl ether (Methoxyflurane) was subjected to trial in man.[8] This paper reports on the anesthetic properties of Methoxyflurane in man and reviews the results of its administration in 100 patients.

## PHARMACOLOGY

*Physical Properties.* Methoxyflurane is a clear, colorless liquid which boils at 104.8 C. ± 0.2 degree at 760 mm. of mercury; the freezing point is — 35 C. with a latent heat of vaporization of 49 cal./gm. It has a specific gravity of 1.4279 ($d_4^{20}$). The compound has a fruit-like odor and is pleasant to inhale. The explosive limits are 4.0 per cent (60 C.), 28 per cent (105 C.); however, at 20 C. in air and oxygen they are 0. The flash point, by the Cleveland open-cup method, is 133 F. However, this compound does not sustain burning at 190 F. Its solubility in water is 0.22 grams/100 grams (98.6 F.), and it is miscible in olive oil in all proportions. Air/blood partition coefficients have not yet been determined. The vapor pressure at 20 C. is approximately 25 mm. of mercury. This compound is stable and is not decomposed by air, light, or alkali. For absolute safety, 0.01 per cent dibenzylamine has been added to prevent acid formation.

Blood concentrations for surgical anesthesia in dogs have been approximately 120 to 160 parts per million, with a persistence of the compound in the blood at a level of about 20 parts per million, even after apparently complete recovery 24 hours after anesthesia.[7] Methods for analysis of concentration in blood and air are under study in the laboratories of The Dow Chemical Company.

The circulation and respiration were well maintained throughout anesthesia in the dog; salivation was minimal to absent and the animal did not exhibit twitching or convulsive movements. Intravenous epinephrine up to 8 gamma/kg. produced only occasional extraventricular complexes and did not cause ventricular fibrillation.[7]

## METHOD OF ADMINISTRATION TO MAN

INDUCTION TECHNIQUES: The nature and time of induction was similar in each technique; however, several techniques are described because of the difference in the mechanical systems of the anesthesia apparatus used.

*The Closed Circle $CO_2$ Absorbing System.* A satisfactory method of administering Methoxyflurane was by the closed $CO_2$ absorption circle system. All cases in which this system was employed were with the Heidbrink Kinetometer machine equipped with the ether vaporizer no. 8 on either the inspiratory or expiratory side of the system. Since the agent is weakly irritating to the tracheobronchial tree, it may be given with oxygen or may be preceded by nitrous oxide and oxygen or a thiopental-nitrous oxide and oxygen sequence. Methoxyflurane was introduced into the system at setting no. 5 using the standard no. 8 vaporizer on the expiratory side of the circle; however, if the vaporizer was on the inspiratory side of the circle, it was introduced using the no. 2 setting. The lower

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setting of the vaporizer on the inspiratory side was used to prevent coughing from too high an initial concentration of the vapor.

The anesthetic induction usually proceeded without excitement, and surgical anesthesia generally was achieved smoothly as determined by the regularity of the respiration and the relaxation of the muscles of the jaw and extremities. If the patient had not received premedication, approximately 14 minutes were required before tracheal intubation could be accomplished with ease. However, the use of succinylcholine or *d*-tubocurarine permitted tracheal intubation within one to three minutes following the introduction of Methoxyflurane.

*Semiclosed with $O_2$ or with $N_2O$ and $O_2$ Added.* A second technique for the administration of this drug was to add it to semiclosed $N_2O$ and $O_2$ anesthesia. $N_2O$ and $O_2$ were given at a flow of 6 liters of $N_2O$ and 2 liters of $O_2$ per minute. Methoxyflurane was added as necessary from a Heidbrink no. 8 vaporizer to reinforce $N_2O$-$O_2$ anesthesia, to control phonation or movement, or to produce the necessary peripheral muscular relaxation.

*Copper Kettle Semiclosed.* This agent has been used via the high flow semiclosed "copper kettle" technique. Induction was begun with 1,000 ml. of oxygen flowing through the kettle, which produced a relatively easily respirable mixture. The flow through the "copper kettle" was then gradually increased to 3,000 ml. per minute. This could not be done too rapidly, however, because the patient would cough owing to too high a vapor concentration. With a slower increase in concentration coughing usually failed to occur. (The "copper kettle" used in these studies was redesigned to allow 3,000 ml. of oxygen to pass through it.) Using this technique, the patient would lose his response to the spoken voice within 9 minutes, and be ready for tracheal intubation within 12–14 minutes. There was minimal "bucking" on the endotracheal tube as it was passed, and if it did occur, it subsided rather rapidly. Excitement or delirium during induction of anesthesia with this agent rarely occurred. Nausea and vomiting did not occur during induction with either technique.

*Open Drop.* Methoxyflurane was allowed to drop on a Yankauer open-ether mask at a rate dependent upon the ability of the patient to respire the mixture. The rate of flow proceeded until surgical anesthesia was obtained, and was then continued at a rate that provided adequate operating conditions without significant depression of blood pressure.

MAINTENANCE: *General Maintenance.* Upon the establishment of surgical anesthesia (with or without tracheal intubation), the administration of the drug was adjusted, depending upon the reaction of the patient to painful afferent stimuli or upon the desired degree of muscle relaxation. A lowered blood pressure, which usually meant overdose, could be reversed within 1–2 minutes by decreasing the concentration of the agent in the inspired mixture, usually without affecting the operating conditions. However, the blood concentration of anesthetic agent appeared critical, since the patient might have profound peripheral muscle relaxation and then move following a small decrease from the critical concentration.

The maintenance of the anesthesia during the first half hour of the procedure appeared to require partially open vaporizers. However, thereafter the anesthetic agent can be turned off or placed in the 1–2 position on the no. 8 Heidbrink vaporizer or at 300 ml. of $O_2$ flowing through the copper kettle vaporizer.

This is a potent anesthetic; however, the safety lies in the fact that its saturated vapor pressure is only 25 mm. of mercury at 20 C. The pupils remained small throughout the induction period and the period of early maintenance, and dilated only in great depth of anesthesia. As soon as the individual could no longer respond to the spoken voice, his eyes became central and fixed, and did not oscillate during light surgical anesthesia.

*Respiration.* There was no change in respiratory rate or tidal volume during the induction phase of anesthesia using this agent. However, all premedication had been accomplished with a barbiturate and belladonna drug. During surgical anesthesia, there was a decrease of respiratory minute volume (R.M.V.), more in tidal volume than in rate. Because of the decrease in the R.M.V., we believe that the patient's pulmonary ventilation should be assisted or controlled during the surgical level of anesthesia. If at any

particular time, painful stimuli are perceived, an increase in respiratory rate occurs.

No increase in mucous or salivary secretions has been observed throughout the induction or maintenance phases. We believe that the compliance of the lung and chest wall increased following administration of this drug, as resistance to inflation of the lungs appeared minimal.

*Circulation.* The effect of this agent on the cardiovascular system was the one significant sign of deep anesthesia or anesthetic overdose. Blood pressure could be maintained at normal levels throughout surgical procedures even with profound abdominal relaxation. However, if the patient did become hypotensive, it was important that the concentration of the anesthetic agent in the inspired mixture be decreased. When hypotension occurred it was usually to a level of 80–90 mm. of mercury systolic.

Cardiac rate slowed slightly in association with a depression in blood pressure. The cardiac rhythm was stable, and we have seen no changes in rhythm other than a wandering pacemaker. We have not observed ventricular complexes in association with the administration of this anesthetic. Abnormal rhythms in a few patients have returned to normal sinus rhythm during the administration of the agent.

Most patients had satisfactory skin color throughout the administration of the anesthesia. A few geriatric patients had an unexplained pallor of the face during surgical levels of anesthesia.

*The Effect of the Anesthetic on the Muscular System.* Any degree of muscle relaxation could be produced by this agent. However, with light levels of anesthesia, muscle relaxation was produced with *d*-tubocurarine or succinylcholine. No changes in blood pressure were associated with the administration of these drugs. The dose-response relationship of *d*-tubocurarine or succinylcholine appears to be similar to that used with diethyl ether.

*The Electroencephalogram as a Guide to Depth.* In light anesthesia with Methoxyflurane, a low voltage pattern of fast activity was seen. During surgical anesthesia a higher voltage pattern of slow activity appeared. This electroencephalographic pattern was unlike that characteristic of diethyl ether, since an immediate transition from fast activity of low voltage to slow activity of high voltage

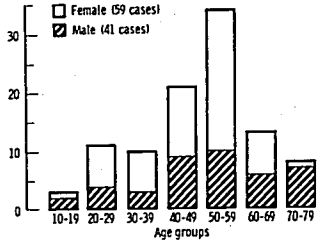


Fig. 1. Age and sex distribution of patients receiving Methoxyflurane.

TABLE 1

TYPE OF SURGERY UNDER METHOXYFLURANE ANESTHESIA

100 PATIENTS

| | |
|---|---|
| Nervous system, extradural | 15 |
| Nervous system, intradural | 19* |
| Head and neck | 9 |
| Upper abdomen | 12 |
| Lower abdomen | 10 |
| Urological | 8 |
| Gynecological | 12 |
| Extremity | 5 |
| Intrathoracic | 6† |
| Extrathoracic | 3 |
| Other | 1 |
| Total | 100 |

* Includes nine hypophysectomies.
† Includes one mitral, one ductus, and four lung.

TABLE 2

COMPARISON OF BROMSULPHALEIN RETENTION FOLLOWING METHOXYFLURANE AND DIETHYL ETHER ANESTHESIA

| Postoperative Day | Ether (18 Patients)* | | Methoxyflurane (13 Patients) | |
|---|---|---|---|---|
| | Normal | Abnormal | Normal | Abnormal |
| Control | 4.3 | 6.4 | 0.9 | 15.6 |
| Third | 25.0 | 29.0 | 11.6 | 37.8 |
| Fifth | 23.0 | 23.8 | 12.7 | 38.4 |
| Tenth | 14.5 | 17.8 | 5.7 | 18.7 |

* Fairlie and associates.[10]

TABLE 3

FOUR DEATHS FOLLOWING USE OF METHOXYFLURANE
100 PATIENTS

| Age | Sex | Anesthesia | Operation | Course | Autopsy | Remarks |
|---|---|---|---|---|---|---|
| 58 | M | Thiopental Succinylcholine Methoxyflurane | Pulmonary lobectomy for carcinoma | Progressive cyanosis and dyspnea; death on third postoperative day | Bronchopheumonia, emphysema and fibrosis | Unrelated to anesthesia, Insufficient functional pulmonary tissue remaining |
| 55 | M | Thiopental Methoxyflurane *d*-Tubocurarine | 1. Hemicolectomy for cancer of colon 2. Reoperation for intestinal obstruction | Progressive renal failure; death 5 days after second operation electrolytic imbalance | Proximal convoluted tubules showed cloudy swelling and disruption and loss of nuclei | Not related to anesthesia |
| 41 | F | Thiopental Methoxyflurane | Exploratory laparotomy for diffuse carcinomatosis | Gradual declining course; death in uremia | Widespread sarcoma | Not related to anesthesia |
| 52 | F | Thiopental Methoxyflurane | Clipping of aneurysm of left middle cerebral artery | Satisfactory immediate postop course, later development of cerebral edema and respiratory and cardiovascular failure; death on third postoperative day | Massive cerebral edema | Not related to anesthesia |

did not occur. However, extreme depth of anesthesia was accompanied by very low voltage or very slow waves of high voltage, both of which gradually became depressed to a straight line. This depth was never necessary during clinical anesthesia. Profound abdominal relaxation occurred when a pattern of rapid activity and low voltage was interspersed with short bursts of high voltage slow waves.

*The Electrocardiogram.* The electrocardiogram indicated normal sinus rhythm in the majority of cases where the anesthetic agent was given and only in one instance was a wandering pacemaker observed. S-T segment depression such as was seen in the dog was not observed in man. Electrocardiographic monitoring indicated to us that the cardiac conducting system is stable during Methoxyflurane anesthesia.

EMERGENCE: The administration of Methoxyflurane should be stopped 10–15 minutes prior to the end of the surgical procedure. This maneuver decreased the emergence time. We have allowed the patient to breathe oxygen during emergence or have attempted Methoxyflurane desaturation with a nitrous oxide-oxygen rapid flow technique.

The emergence was quiet without delirium. Postanesthetic hypotension related to the anesthetic agent has not been seen. Nausea and vomiting were minimal, and appeared less than seen with commonly used anesthetic agents.

TABLE 4

COMPLICATIONS FOLLOWING THE USE OF METHOXYFLURANE
100 PATIENTS

| Age | Sex | Operation | Course | Remarks |
|---|---|---|---|---|
| 67 | M | Bilateral chordotomy for intractable pain from metastatic carcinoma | Hypotension for 2 days following operation; treated with vasopressors; discharged improved | Hypotension probably related to sympathectomy at time of chordotomy |
| 51 | M | Decompression of trigeminal nerve | Benign postoperative course; readmitted with Guillain-Barré syndrome 10 days after operation; satisfactory course | Not related to anesthesia |
| 44 | M | Right pneumonectomy for carcinoma | Tension pneumothorax on third postoperative day; supraventricular tachycardia on sixth postoperative day; responded to digitalization | Not related to anesthesia |
| 75 | M | Transurethral resection for benign prostatic hypertrophy | Uneventful course until septicemia on third postoperative day; responded to antibiotics | Not related to anesthesia |

## Results

There were 41 males and 59 females in this series whose ages ranged from 10 years to 79 years (fig. 1). These patients underwent operative procedures as indicate in table 1. Bromsulphalein retention studies were performed on 13 patients and the results compared to a similar study by Fairlie and associates [10] who used diethyl ether (table 2). Ninety-two patients had a completely uneventful postoperative course. There were four deaths (table 3) and four complications (table 4). None of the deaths or complications was believed to be related to the administration of Methoxyflurane.

## Discussion

This is the first unsymmetrical methyl ethyl ether used for clinical anesthesia in man. It is nonexplosive and nonflammable at 20 C. in all concentrations in air as well as in oxygen. In our experience, induction has been smooth and without incident, anesthesia maintenance easily controllable, and depth of anesthesia readily reversible. This agent appears to be a complete anesthetic in that profound muscle relaxation can be produced and the depth of surgical anesthesia regulated at will. Cardiac rhythm has been stable. Intravenous epinephrine in doses up to 8 gamma/kg. did not produce ventricular fibrillation during administration of this agent in the dog.[7] The absence of postoperative delirium and hypotension is, we believe, a good feature of this drug. The fact that it can be used as a total anesthetic by itself or as part of a balanced technique makes this a versatile agent. There is no increase in capillary bleeding during surgery. This drug depresses the blood pressure by a mechanism not yet understood. The depression of blood pressure appears to be the most reliable sign of anesthesia depth or overdose, and should be a warning to decrease the concentration of the anesthetic agent in the inspired mixture.

The need for postoperative narcotics appears diminished, but this should be studied statistically. The premedication need not be changed from that used prior to other anesthetic agents, although narcotics may cause respiratory depression during anesthesia with this agent. Anesthesia can be conducted for several hours with small quantities of the compound; after the first hour of anesthesia, the amount necessary to maintain a desired level is almost negligible using the closed system.

Although this is a potent anesthetic agent, we believe there is safety in the low saturated vapor pressure and difficulty of vaporization. The slow induction is most likely due to the high boiling point and low saturated vapor pressure, and the small amount of agent required for anesthesia is due to its high potency following vaporization. The prolonged emergence is probably due to the high fat solubility with subsequent slow release of the agent into the blood, thus maintaining an anesthetic concentration in the brain.

The pharyngeal and tracheal reflexes are obtunded and the patient may move before reacting upon an airway or endotracheal tube. Extubation at the end of operation has not been accompanied by laryngeal spasm in our experience.

We have seen no untoward reaction using this drug with *d*-tubocurarine or succinylcholine. The effect shown by liver function tests is about the same as diethyl ether. We have not studied the effect of Methoxyflurane on renal or hemopoietic mechanisms.

## Summary

A nonexplosive and nonflammable fluorinated unsymmetrical ether, Methoxyflurane, has been studied in 100 patients. This agent was administered by open drop, semiclosed, closed, or nonbreathing systems. Premedication was with a barbiturate and a belladonna derivative. The induction was smooth and emergence without dilirium or hypotension. We have not seen ventricular arrhythmias during administration of this drug, but have observed definite electroencephalographic changes associated with increasing depth of anesthesia. Nausea and vomiting and the need for analgesic medication appeared decreased in the immediate postanesthetic period.

Original samples of the material were synthesized by The Dow Chemical Company. The current clinical supply was received from Department

of Medicine, Abbott Laboratories, North Chicago, Illinois.

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**OBESITY** Overweight of 10 to 20 per cent is associated with a significant elevation of mortality and the incidence of excess mortality increases with the degree of overweight. The excess death rate is caused uniformly by diseases of the heart and circulatory system, diabetes and biliary tract disease. In the overweight, systolic and diastolic blood pressures are elevated in all age groups; arteriosclerotic and ischemic heart disease appear to be more prevalent; coronary heart disease and diabetes were more common; and gall bladder function was more likely abnormal. Pulmonary function studies in 28 patients who were 100 pounds or more above ideal weight revealed 15 to have abnormally low arterial oxygen saturation and 10 of these to have lung disease. Distinct improvement was noted when weight was reduced. The overweight surgical patient offers special problems both to the anesthesiologist and to the surgeon. These include difficulty in maintaining a free airway, inadequate respiratory exchange, longer induction and recovery period and need for greater muscular relaxation. Also cited is the increased frequency of postoperative embolism and thrombosis. (*Marks, H. H.: Influence of Obesity on Morbidity and Mortality, Bull. New York Acad. Med. 36: 296 (May) 1960.*)

**TEMPERATURE REGULATION** Dehydration raises the thermal threshold for sweating, heat storage correspondingly increases, and each increment in body temperature provides additional stimulation to the regulatory mechanism whose reactivity is diminishing. An increasingly precarious equilibrium is almost attained between heat exchanges with the environment and heat production in the body, but at the expense of progressively higher body temperatures. In this sense, dehydration elicits failure in temperature regulation during exposure to heat. (*Hertzman, A., and Ferguson, I.: Failure in Temperature Regulation during Progressive Dehydration, U. S. Armed Forces Med. J. 11: 542 (May) 1960.*)