Methoxyflurane—A Clinical Evaluation

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METHOXYFLURANE, an ethyl methyl ether, has been evaluated clinically by others[1, 2, 3] and in our laboratory was found to be an anesthetic capable of producing irreversible changes in the animal when sufficiently high concentrations were employed. It depressed respiratory exchange progressively as anesthetic concentrations were increased; it induced a progressive reduction in blood pressure as the plane of anesthesia became deeper; it produced virtually no changes in cardiac rhythm; only under certain circumstances was it capable of sensitizing the myocardium to epinephrine with the production of hazardous ventricular arrhythmias; and hepatic changes following chronic exposure to anesthetic concentrations for 15 hours were similar to those found with halothane under comparable circumstances.[4, 5]

Following this laboratory experience, a clinical evaluation was undertaken. In 75 surgical procedures, most of which required profound muscle relaxation, methoxyflurane was administered without ancillary relaxant drugs during the operation. The patients' ages ranged from 13 to 77 years and all but three were classified in physical status I or II; two patients were in status III and one in VI. Preoperative medications consisted of either a short-acting barbiturate or a narcotic drug and an anticholinergic agent in dosages consistent with the age and condition of the patient.

Induction of Anesthesia

Because of the high boiling point of methoxyflurane (104° C.) and the resultant low vapor pressure at room temperatures, an efficient vaporizer and time were required to induce narcosis. In the first 18 patients anesthesia was induced by mask, employing a no. 8 Heidbrink ether vaporizer on the inhalation side of a circle system, utilizing a 2 liter flow of oxygen and a 2 or 4 liter flow of nitrous oxide. It was found that: (1) the fruity odor of methoxyflurane was acceptable to most patients; (2) the vaporizer could be turned fully on quite rapidly, although the vapor was irritating if introduced too quickly; (3) maximum utilization of the vaporizer was necessary to induce anesthesia; (4) a short-lived excitement stage was present; (5) secretions were minimal; and (6) laryngospasm was absent unless endotracheal intubation was attempted in too light a plane of anesthesia.

The average time required to produce satisfactory anesthesia and relaxation for endotracheal intubation in this group was 13.2 minutes, with a range of 10 to 25 minutes. On three occasions succinylcholine was administered when endotracheal intubation failed on the first attempt, and coughing with laryngospasm ensued as the level of anesthesia lightened.

In a second group of eight patients, methoxyflurane was vaporized in a 'copper kettle' directing the maximum flow of 1,000 ml. of oxygen through the kettle and diluting the vapor with low outside flows of nitrous oxide and oxygen. This technique did not produce sufficient anesthetic vapor to induce surgical anesthesia. Four patients had induction periods longer than 20 minutes, and all required succinylcholine in order to perform endotracheal intubation.

In an effort to shorten the induction period, the remaining 49 patients were given an hypnotic dose of thiopental (average 175 mg.), and then methoxyflurane was vaporized from a Heidbrink ether vaporizer as above. About 60 per cent of this group were given succinylcholine 40 to 60 mg. intravenously to facilitate insertion of the endotracheal tube

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The tracheas of the remaining 40 per cent were intubated atraumatically without muscle relaxant, but after the transtracheal topical injection of hexylcaine 100 mg. The average induction time in this group was 13 minutes (range of 5 to 20 minutes).

Respiratory depression was noted soon after third stage anesthesia was reached. Spontaneous respiratory activity could be abolished readily by assisting respiratory exchange, and at a plane when sensory stimulation of the patient produced reflex movement.

Blood pressure reductions were common as surgical anesthesia was induced, the degree of hypotension being dependent on the concentration breathed by the patient. The average reduction in systolic pressure after endotracheal intubation in this series was 15 mm. of mercury. The most profound hypotension was seen in hypertensive patients. In three instances a reduction of 60 mm. of mercury in systolic pressure occurred: this hypotension was treated successfully by turning off the vaporizer and by the administration of methamphetamine 5 to 10 mg. intravenously.

Maintenance of Anesthesia

Once a surgical plane of anesthesia had been established, adequate surgical conditions with profound muscular relaxation could be maintained by keeping the vaporizer open between the 0.5 and number 3 settings. With a gas flow of oxygen 2 liters and nitrous oxide 2 liters per minute, the inhaled vapor concentration of methoxyflurane under these circumstances varied between 0.2 and 0.4 volumes per cent.

The respiration of the majority of patients was controlled to facilitate surgical procedures and because the patients showed little tendency to breathe spontaneously in the presence of adequate ventilation. In three patients the Stephenson respirator was used satisfactorily.

Since the conventional signs for determining depth of anesthesia were absent with methoxyflurane, the level of anesthesia was followed clinically by the response of the blood pressure to an increase or decrease of drug concentration. A reduction in systolic pressure following upon an increase in vapor concentration responded readily to a reduction in concentration. In this series, almost cadaveric muscle relaxation could be obtained while maintaining a clinically adequate systolic blood pressure. During the surgical procedures, the average reduction in systolic pressure from the preoperative reading was 12.3 mm. of mercury, while a small increase of 1.2 mm. of mercury occurred in the diastolic pressure.

Changes in position of the anesthetized patient produced a significant hypotension on three occasions. Reflex hypotension secondary to visceral fraction (stomach or uterus) was unusual. Blood loss occurring during operation was reflected rather quickly by a reduction in blood pressure: methoxyflurane did not mask blood loss.

To determine the reaction of patients under methoxyflurane anesthesia to vasopressor drugs, methamphetamine 5 to 10 mg., metaraminol 2 mg., methoxamine 2 to 5 mg., and phenylephrine 0.5 mg were administered intravenously on elective occasions. These compounds produced the anticipated elevation of systolic pressure and without associated changes in the electrocardiogram other than occasional sinus bradycardia.

In the majority of patients, the pulse rate changed little during the course of anesthesia. However, in 3 patients a tachycardia of 120 to 130 per minute, not associated with blood loss or anticholinergic drug administration, developed early during operation and persisted throughout the procedure.

The average duration of anesthesia in this series was 2 hours and 50 minutes, with a range between 20 minutes and 8½ hours. In an attempt to shorten the reported lengthy recovery period after methoxyflurane administration, the drug was discontinued and high flows of oxygen and nitrous oxide initiated an average of 35 minutes prior to the end of operation. In intra-abdominal procedures, methoxyflurane vaporization was stopped as the closure of the peritoneum was begun. It was not necessary in any patient to supplement muscle relaxation with succinylcholine to facilitate closure.

At the conclusion of the surgical procedure, all patients were breathing spontaneously and adequately, or did so within 10 minutes. Laryngeal and pharyngeal reflexes were present, although nasopharyngeal airways could be tolerated readily.

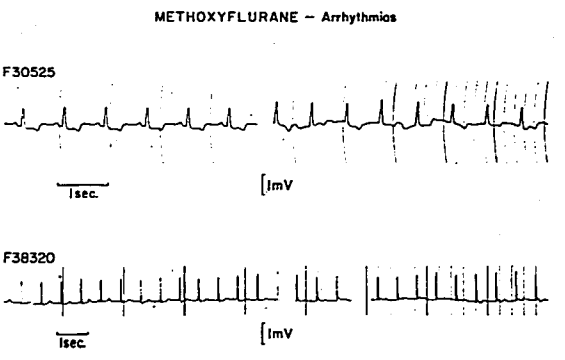

FIG. 1. ECG tracings (lead 2) from two patients under methoxyflurane anesthesia.

Postoperative Period

The average recovery time from the end of operation until the patient could respond intelligently to questions, was 1 hour and 23 minutes, with a range of 15 minutes to 4 hours. However, in 11 of the first 18 patients, the recovery time was more than 1½ hours, whereas in the last 57 patients, recovery time was more than 1½ hours in only 9. As more experience was gained in administration of the drug, the recovery time was shortened.

The incidence of nausea and vomiting postoperatively was 26 per cent. One patient, a 47 year old woman with ovarian carcinoma, had persistent vomiting for 3 days after an anesthetic lasting 1½ hours.

Postoperative analgesia, *i.e.*, the time interval before a narcotic was administered for pain, lasted an average of 6.8 hours, with a range from 2 to 21 hours.

Two patients developed copious respiratory tract secretions in the recovery room which required repeated aspiration. One of these patients developed a pneumonitis which responded adequately to therapy.

One postoperative death occurred in this series. A 67 year old woman, with obstructive jaundice and arteriosclerotic heart disease with angina, was exposed to two hours of methoxyflurane anesthesia while an exploratory laparotomy was performed. Carcinoma of the ampulla of Vater was found and a definitive surgical procedure was not accomplished. During induction of anesthesia, the systolic blood pressure fell from 120 to 75 mm. of mercury, but was restored to normal with administration of a vasopressor drug. The immediate recovery period was uneventful, but 10 hours postoperatively, shortly after administration of dihydromorphinone 2 mg., cardiovascular collapse occurred. The electrocardiogram was indicative of subendocardial ischemia. Vasopressor drugs were required to maintain the blood pressure, and she expired on the sixth postoperative day. Autopsy was not obtained.

Vapor Concentrations

In 20 patients, samples of inspired gas and vapor, withdrawn from the accordion tubing of the gas machine on the inhalation side, were analyzed in a Perkin-Elmer vapor fractometer * to determine the concentration of methoxyflurane vapor. In the laboratory it had been determined that the maximum concentration of vapor which could be obtained from the no. 8 Heidbrink ether vaporizer with wick in place and at room temperature, utilizing a gas flow of 4.0 l./minute in a circle system, was 1.6 volumes per cent. Determinations in patients showed that during induction of anesthesia a minimum of 1.0 volume per cent of methoxyflurane vapor was required for the production of surgical anesthesia. Concentrations required during maintenance of anesthesia varied between 0.2 and 0.5 volume

* Model 154-C, Perkin-Elmer Corporation, Norwalk, Ohio. A one meter column of diisodecyl phthalate on fire brick was used at a temperature of 110° C., with helium as carrier gas. Flow was not critical.

per cent. Utilizing a semiclosed circle technique, with the ether vaporizer on the inhalation side as described above, these concentrations could be maintained with the vaporizer open to a setting somewhere between the 0.5 and 3 marks.

Monitoring Procedures

In the first 20 patients of this series, the electrocardiogram and electroencephalogram were recorded continuously. Only supraventricular arrhythmias were seen in the electrocardiogram, consisting primarily of various types of nodal rhythm (fig. 1). These arrhythmias were noted in four of the 20 patients. However, in two patients who were not being monitored, irregularities were noted for short periods of time on palpation of the pulse. It was believed that these irregularities represented ventricular arrhythmias.

Surgical planes of anesthesia that were adequate clinically and which provided good muscular relaxation were reflected in the electroencephalogram by rapid low-voltage activity. However, large delta waves and burst-suppression activity were seen when higher concentrations of methoxyflurane were administered (fig. 2).

Bromsulphalein Dye Retention

As a measure of liver function, the degree of bromsulphalein dye retention was determined in 50 patients preoperatively, and 48 hours and 6 days following anesthesia and operation. Forty-three of these patients were subjected to intra-abdominal procedures. The average duration of anesthesia was 2 hours, 56 minutes (± 1 hour, 14 minutes). The average preoperative dye retention was 5.4 (± 9.3) per cent; on the second postoperative day the average value had increased to 18.8 (± 12.3) per cent; on the sixth postoperative day the average days retention was reduced to 9.9 (± 7.9) per cent. There was little correlation between the degree of bromsulphalein retention and the duration of anesthesia, nor with the type of operative procedure.

TABLE 1. Elevated BSP After Anesthesia

Anesthetic	No. Patients	Per Cent Abnormal	
		Second Postoperative Day	Sixth Postoperative Day
Methoxyflurane	37	94	57
Ether	13	67	69
Cyclopropane	6	83	20
Halothane	5	80	50
Spinal	8	38	57

Thirteen of the patients had elevated BSP retention (greater than 5 per cent after 45 minutes) prior to operation. In six of these patients values returned to or below the initial values within six days. One was the patient who died postoperatively, and three were discharged before the sixth day. None of the other four presented any clinical evidence of liver disease. Of the remaining 37, 94 per cent had abnormal BSP values on the second postoperative day. By the sixth postopera-

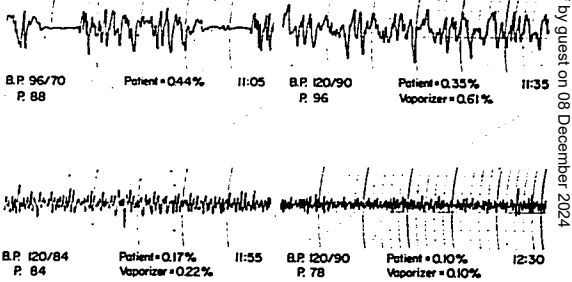

FIG. 2. EEG tracing from patient under methoxyflurane anesthesia. Recordings were not made during induction—the first tracing reflects deepest stage of anesthesia attained. Note the relative independence of EEG depression and blood pressure. The final tracing was obtained while the patient was moving on the operating table. "Patient" concentrations determined on expiration at endotracheal tube. "Vaporizer" concentrations, in corrugated tubing on inhalation side.

tive day 57 per cent still had increased retention. This corresponds to the results in a limited series of similar procedures with other anesthetic agents (table 1). Comparable results following anesthesia have been reported previously.[6, 7, 8]

Discussion

Since methoxyflurane is both a fluorinated compound and an ether, it might be well to compare its actions with those of the recently accepted halothane and the long-established ethyl ether.

(1) The induction period with methoxyflurane is comparable in duration with that of ethyl ether, but for a different reason. Methoxyflurane is not highly irritant and therefore the induction is usually smooth: the length of induction is due to the high boiling point and consequent difficulty in vaporizing the drug.

(2) The respiratory and cardiovascular depression are comparable to that seen with halothane. However, a narrowing of the pulse pressure is seen more consistently with methoxyflurane than with halothane.

(3) The muscular relaxation associated with methoxyflurane administration is more profound than that obtained with ethyl ether in comparable planes of anesthesia. This relaxation is one of the most striking properties of methoxyflurane.

(4) The recovery time following methoxyflurane anesthesia is similar to that of ethyl ether. The high oil-water coefficient ratio for methoxyflurane (400) no doubt prolongs its elimination from the patient. During this recovery period, the patient can be roused and the protective laryngeal reflexes are active.

(5) The duration of apparent postanesthetic analgesia following methoxyflurane is about the same as that following ethyl ether administration, and much longer than after halothane.

(6) The incidence of postoperative nausea and vomiting (about 5 per cent) after methoxyflurane anesthesia lies midway between that encountered with ethyl ether and halothane (about 12 per cent).

(7) Methoxyflurane anesthesia transiently depresses liver function (as estimated by bromsulfalein retention) in a manner similar to ether and halothane.

Summary

Clinical experiences with the administration of methoxyflurane for anesthesia to 75 patients are discussed. The potency of this drug is counterbalanced by its high boiling point and the difficulty in providing anesthetic vapor concentrations. Induction of anesthesia is relatively slow and recovery may be prolonged. Profound muscular relaxation can be provided in planes of anesthesia which do not compromise cardiovascular function. Dangerous cardiac arrhythmias have not been observed during administration. Liver function studies indicate that, while dysfunction may occur, the abnormalities seen are temporary in nature and no greater than those observed with other anesthetic drugs under comparable circumstances.

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