METHOXYFLURANE: A CLINICAL EVALUATION OF ITS EFFECTS, BASED ON FIVE HUNDRED CASES

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METHOXYFLURANE,† the nonflammable anesthetic agent, has been administered to more than 2000 patients at the Cleveland Clinic Hospital. Wasmuth and associates[1] reported a clinical evaluation of the use in 206 cases; our report is an evaluation of 500 additional consecutive cases from near the end of the series. The cases are an unselected series comprising various operative procedures (*Table 1*). The ages of the patients ranged from 6 months to 74 years, the mean age being 45 years; the ages of 50 patients (10 per cent) ranged from 6 months to 14 years.

Table 1.—*Surgical procedures in 500 patients who received methoxyflurane anesthesia*

Type of surgical procedure	No. of patients
Plastic	120
General	105
Vascular	100
Gynecologic	85
Orthopedic	45
Genitourinary	20
Thoracic	15
Neurosurgical	5
Obstetric	5
Total	500

Technic of Administration

Methoxyflurane was administered in one of two ways: by vaporization in a No. 8 Heidbrink wick vaporizer, or by open-drop technic. The semiclosed and closed technics were used. The majority of anesthetics were administered with the No. 8 Heidbrink wick vaporizer.

The patients were premedicated either with morphine sulfate or with meperidine hydrochloride, atropine, and a barbiturate. In most cases intubation was used after

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a thiopental sodium—succinylcholine—oxygen sequence. The volume of gas flow was in most cases 4 l., utilizing 2-l. volumes of nitrous oxide and oxygen. The vaporizer was opened to the first, or number 1 position, and then was rather rapidly advanced to the number 5 or number 6 position. If the patient were allowed to breathe spontaneously, the induction would be prolonged. However, when the respirations were assisted, a plane of surgical anesthesia could be reached within 10 minutes, as evidenced by a gradual fall in blood pressure and by an increase in muscular relaxation and compliance. At this point the concentration of methoxyflurane was reduced to a position of 2 or 3 on the No. 8 Heidbrink wick vaporizer, and the blood pressure was closely observed until stabilization occurred. This concentration of methoxyflurane usually kept the patient in a satisfactory maintenance plane of anesthesia.

It has been our experience that the blood pressure is the most reliable guide to the depth of anesthesia with methoxyflurane. From the onset of administration the blood pressure falls as the level of anesthesia deepens, and we have occasionally observed a drop to 80 mm. of Hg in deep anesthesia. This can easily be reversed by lightening the anesthesia. Even at the pressure of 80 mm. of Hg, the patient's skin remains warm and dry, and there is little increase in the pulse rate. When it is desirable during induction to elevate low blood pressures, vasopressors should be used rather than reducing the concentration of methoxyflurane in order that surgical planes of anesthesia may be reached quickly.

Open-drop technic. In 20 children the open-drop technic was used; most of these children were less than one year of age. The procedures ranged from appendectomy to a change of a surgical burn dressing (*Table 2*). A Yankauer mask with from six to eight layers of gauze was used. A wick was placed in the methoxyflurane container, and induction was started as it is with diethyl ether. A much smaller amount

Table 2.—*Surgical procedures performed in 20 children under methoxyflurane-induced anesthesia by open-drop technic*

Procedure	No. of cases
Herniorrhaphy	4
Cast change	4
Skin graft	3
Suture removal	3
Appendectomy	2
Burn dressing change	2
Suprapubic cystotomy	1
Tenotomy	1
Total	20

(than diethyl ether) of methoxyflurane was found to be necessary for induction and maintenance: 20 to 30 drops per minute for induction, and 10 to 12 drops per minute for maintenance. Profound analgesia was achieved in from three to five minutes.

Respiratory response. The respiratory response usually was not altered either in rate or in depth in light planes of anesthesia. The respirations could easily be taken over in deep planes and could be controlled where indicated. When controlled respiration was used, the concentration of methoxyflurane was reduced in order to avoid deepening of the level of anesthesia and lowering of blood pressure. In light surgical planes of anesthesia the tidal volume was decreased only slightly, while in deep planes there was a definite respiratory depression.

Cardiac response. The cardiac response to methoxyflurane was extremely stable. In the 500 cases of this review, no abnormality in cardiac rhythm was noted. In many patients who had abnormalities in cardiac rhythm before induction of anesthesia a reversion to normal sinus rhythm occurred upon administration of methoxyflurane.

Methoxyflurane was used in combination with a variety of vasopressor drugs without demonstrable cardiac incompatability. A stability of cardiac action during methoxyflurane anesthesia in the presence of epinephrine and norepinephrine can be shown by the following examples. In plastic operations, methoxyflurane was used with epinephrine (1:50,000) in procaine (1.0 per cent) for local infiltration with only a rise in pulse and blood pressure to indicate the presence of epinephrine effect. During vascular procedures norepinephrine, 8 mg. (1 ampul) in 1000 ml. of 5 per cent dextrose in water, intravenously at a rate of from 2 to 6 ml. per minute was used to support blood pressure without causing demonstrable cardiac irregularities.

Relaxants. The administration of relaxants was necessary during upper abdominal, thoracic, and a few of the lower abdominal procedures in this series. In all cases the amount of relaxant used during methoxyflurane-induced anesthesia was similar to that necessary during diethyl-ether-induced anesthesia for the same procedure. The use of succinylcholine in combination with methoxyflurane had no great effect on blood pressure. However, when d-tubocurarine was given in the usual dosages per pound of body weight, profound drops in blood pressure occurred (*Fig. 1A and B*), indicating the necessity of reducing the dosage of d-tubocurarine to about one third.

Analgesia. The analgesic properties of methoxyflurane are profound. The usual concentrations of methoxyflurane administered were of the order of 2.0 per cent to produce, and 0.25 per cent to maintain surgical anesthesia. It has been our experience that a small amount of methoxyflurane (0.25 to 0.5 per cent), added to a thiopental sodium—nitrous oxide sequence smooths out an otherwise uneven anesthetic to the point where no more thiopental sodium need be given, and postanesthetic emergence is not unduly prolonged.

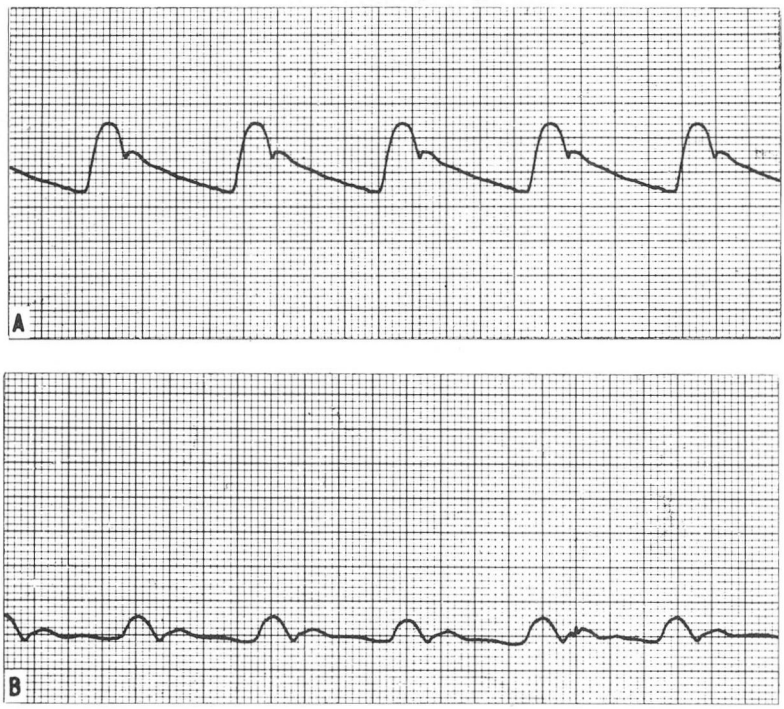

Fig. 1. A, Graph showing blood pressure of 130/90 mm. of Hg after 15 minutes of methoxyflurane administration. B, Graph showing reduction in blood pressure to 50/40 mm. of Hg six minutes after administration of 0.15 mg. of d-tubocurarine per pound of body weight.

Postanesthetic emergence. Prolonged emergence (more than one and one-half hours) could be avoided in almost all instances when the methoxyflurane was discontinued from 30 to 40 minutes before the completion of the operative procedure. Early in the clinical evaluation of this new agent the anesthesia was continued to the end of the operative procedure, and emergence was prolonged in some cases as long as one and one-half to two hours. Recently, 80 per cent of the patients awoke on the operating table, and responded to vocal commands. When, however, they were allowed to remain quietly in the recovery room they went into an arousable sleep. The residual analgesia of the methoxyflurane was evidenced by the small amount of analgesic agents these patients required in the first two hours postoperatively.

The average duration of the procedures in this series was two and one-quarter hours, and the average duration of methoxyflurane administration was one and three-quarter hours. The average time of emergence to response to vocal commands, in all cases was 28 minutes, and time to awaken fully and to be oriented in time and place was one and one-quarter hours.

In the recovery room the patients were quiet, often sleeping. They were pale, but had warm dry skin. Often there was some degree of cyanosis of the nailbeds. Respirations were adequate unless there was some residual activity of relaxants. Most patients responded to oral instructions to move, to breathe deeply, and to cough. Those requiring oropharyngeal airways because of partial obstruction, tolerated them extremely well even though in possession of their vital reflexes. In the recovery room the incidence of nausea was 3 per cent, and of vomiting 2 per cent.

Amounts of methoxyflurane used per hour of surgery. In 50 cases volume studies were done to determine the average amount of methoxyflurane used per hour. Before the methoxyflurane was placed in the No. 8 Heidbrink wick vaporizer, the volume of the agent was measured in a graduated cylinder. At the end of the surgical procedure the methoxyflurane remaining in the vaporizer was drained out and then was measured in the same graduated cylinder. In the computations, allowances were made for the amount of methoxyflurane remaining on the wick. With the semiclosed technic at gas flow rates of 4 l. per minute, the average amount used per hour of surgical procedure was 8.37 ml., with 12.20 ml. and 3.60 ml. at the upper and the lower extremes.

Summary

Methoxyflurane, a halogenated methyl-ethyl ether, has been used in more than 2000 patients at the Cleveland Clinic, 500 of whom have been evaluated in this report. Methoxyflurane is in increasingly greater use by our anesthesiologists because of: ease of administration, nonflammability, production of profound analgesia, compatability with a variety of vasopressors. These advantages offset its relative disadvantages of slow induction and prolonged emergence. With experience these relative disadvantages can be overcome also, and in some cases the longer emergence may be used to advantage.

Reference

1. Wasmuth, C. E., and associates: Methoxyflurane—new anesthetic agent; clinical evaluation based on 206 cases. Cleveland Clin. Quart. **27:** 174-183, 1960.