Halopropane—A Clinical Evaluation

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Halopropane is a noninflammable volatile liquid which has been found to possess properties of general anesthesia. Experiences in animals and in man have indicated that the drug is capable of producing adequate surgical relaxation and reasonably prompt induction and recovery. Experimental studies in the laboratory with dogs have indicated that it sensitizes the heart to the intravenous injection of epinephrine in a manner similar to halothane and cyclopropane. Eighty-two patients undergoing various surgical procedures were studied. Adequate operating conditions were obtained in all. However, the incidence of arrhythmias was sufficiently great that the drug was considered not completely satisfactory for clinical anesthesia in man. The uptake and excretion of halopropane from the blood was examined in 10 patients, and it was found that the blood level fell slowly, suggesting that the drug is highly soluble in fat. Because of the number of cardiac arrhythmias, some very severe, seen in these patients, it is concluded at this time that the drug probably is not a useful anesthetic agent.

SINCE the introduction of halothane in 1956, many fluorinated ethanes, propanes and ethers have been synthesized for anesthetic use. This report describes experiences with 3-bromo-1,1,2,2-tetrafluoropropane (halopropane), which in early investigations showed promise of fulfilling desirable attributes of chemical stability, nonflammability, volatility, and safety in administration.

Halopropane is a clear, colorless liquid with a boiling point of 74° C. and a vapor pressure at 20° C. of 88 mm. of mercury; the blood/gas partition coefficient is 5.8, the oil/gas ratio is 323, and the oil/water distribution coefficient is 150.[1] It is stable in the presence of soda-lime, and in animals and man has shown no significant deleterious effects on liver or kidney.[2, 3]

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Preliminary investigations in dogs in our laboratory revealed findings similar to those observed by Merkel and Eger.[1] Inhalation of progressively increasing vapor concentrations produced depression of respiration, moderate slowing of pulse rate, and reductions in systolic and diastolic blood pressures. The sequence of events was similar to that noted with halothane. However, cardiac arrhythmias, particularly premature ventricular contractions in the form of bigeminy, were seen more frequently with halopropane than with halothane under comparable conditions. This observation led to a comparison of the incidence of ventricular fibrillation, when dogs were challenged with epinephrine, during light and deep anesthesia induced by several drugs (table 1). In these experiments anesthesia was induced with thiopental 15 mg./kg. intravenously. Light anesthesia was considered the stage at which a lid reflex was just present, and deep anesthesia was believed present when the electroencephalogram showed burst-suppression. The challenging dose of epinephrine (5 to 50 μg./kg.) was dissolved in 5 ml. of 5 per cent dextrose in water and injected over a period of 50 seconds into the femoral vein.[4] Under these conditions, dogs showed a high incidence of ventricular fibrillation, both in light and deep halopropane anesthesia.

Clinical Data

Methods. Eighty-two patients ranging in age from 9 to 74 years, with an average age of 40 years, were included in the study. Numerous types of operations were performed, including intra-abdominal, neurosurgical and intrathoracic procedures. After conventional premedication, anesthesia was induced with a sleep dose of an ultrashort-acting barbiturate. A mask was applied with a flow of 2 liters of nitrous oxide and 2 liters of oxygen. Halopropane was vaporized, beginning immedi-

ately, by means of a Copper Kettle or Vernitrol apparatus, the flow of oxygen through the vaporizer being increased at a rate of 100 ml. every 5 to 6 breaths; the highest such flow of oxygen required for induction was 1,200 ml., which corresponded to a halopropane concentration of 3.9 volumes per cent delivered from the gas machine (chromatographic calibration had shown that 17.5 ml. of halopropane vapor were delivered for each 100 ml. of oxygen passing through the vaporizer). In the majority of patients anesthesia was induced satisfactorily with an inhaled concentration of 3.4 volumes per cent of halopropane.

After several minutes at peak concentration, and when tidal volume began to decline, succinylcholine 40 to 60 mg. was injected intravenously and endotracheal intubation accomplished. In most instances anesthesia was maintained with controlled respirations, employing inhaled concentrations of halopropane which varied from 1.8 to 0.4 volumes per cent. As anesthesia progressed, lesser concentrations of drug were required to maintain adequate operating conditions. The duration of anesthesia varied between 30 and 450 minutes, the average length was 210 minutes.

This anesthetic sequence was pursued for the following reasons. In pilot experiences the omission of nitrous oxide from the inhaled mixture led to a prolonged and vigorous second stage of anesthesia; this excitement stage could be minimized by an intravenous induction with barbiturates and of nitrous oxide. Endotracheal intubation could be accomplished without muscle relaxant drugs, but in so doing the induction time was prolonged 15 to 20 minutes, and even after this period the patient usually reacted by bucking or breath-holding for 2 to 3 minutes following the passage of the tube. Spontaneous respirations were not believed desirable because in surgical planes of anesthesia the tidal volume was reduced significantly.

In 20 patients alveolar samples were withdrawn at intervals during the expiratory phase of respiration from a polyethylene catheter lying just beyond the distal end of the endotracheal tube. These samples were analyzed in a Perkins-Elmer vapor fractometer and the halopropane concentration determined in volumes per cent. In 10 patients arterial blood samples were withdrawn simultaneously with alveolar samples to determine the blood concentration of halopropane. For this purpose exactly 2 ml. of blood from a constant volume heparinized syringe was aspirated into a B-D Vacutainer tube which already contained 2 ml. of tetrachloroethylene. The test tube was shaken vigorously for 15 minutes and then centrifuged at 3,000 r.p.m. for 5 minutes. One microliter of the tetrachloroethylene extract was withdrawn and injected into the gas chromatograph. A one meter column of 20 per cent Dow-Corning silicone oil "200" on 60–80 mesh fire brick was used with a column temperature of 125° C., a helium flow rate of 100 ml. per minute, and a katharometer detector. Standards were prepared by volumetric dilution of liquid halopropane and tetrachloroethylene. Recovery from known blood concentrations, expressed as mg. per cent, ranged from 95 to 102 per cent, so that extraction from the blood was assumed to be complete.

The electrocardiogram was monitored in all but 3 patients, and the electroencephalogram

TABLE 1. Ventricular Fibrillation in Dogs

Anesthetic	Dogs	Challenging Dose Epinephrine μg./kg.				Total Dogs Fibrillating
		5	10	20	50	
Ethyl ether (deep)	7	0	0		0	0/7
Methoxyflurane (light)	10	0	0		1	1/10
Methoxyflurane (deep)	11	0	2		4	6/11
Cyclopropane (light)	5	0	1	0	0	1/5
Cyclopropane (deep)	5	3	1	0	1	5/5
Halothane (light)	5	0	0	1	0	1/5
Halothane (deep)	5	3	1	1		5/5
Halopropane (light)	17	12	2			17/17
Halopropane (deep)	5	2	2	0		5/5
Chloroform	5	4	1			5/5

Response to epinephrine challenge during light or deep anesthesia with ethyl ether, methoxyflurane, cyclopropane, halothane, halopropane, and chloroform.

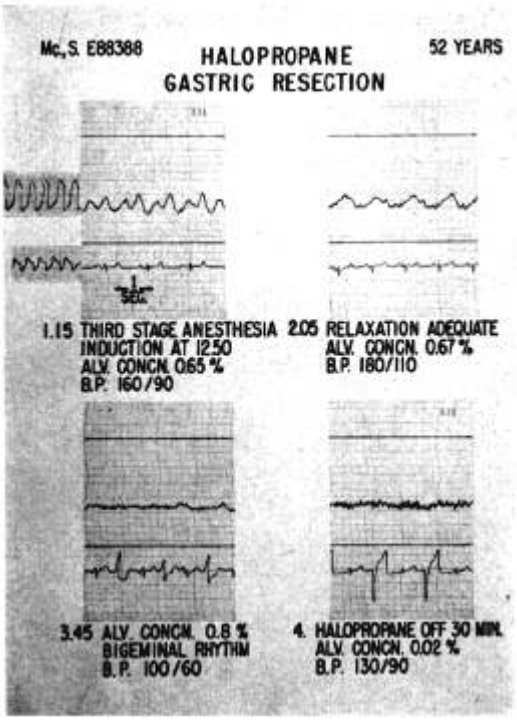

FIG. 1. In upper tracings note high voltage slow waves superimposed on fast activity. In lower 2 tracings note fast activity.

in approximately 50 per cent. In 10 patients, utilizing a Grass Polygraph, arterial blood pressure was recorded continually from a brachial or radial artery by means of an indwelling Cournand needle and a Statham transducer, along with the electrocardiogram and electroencephalogram.

In 6 patients arterial blood samples were collected at intervals of 30 to 60 minutes and *p*H, P_{CO_2} and P_{O_2} were determined on an Instrumentation Laboratory Model 113 analyzer.

Results: Satisfactory anesthesia was obtained in all patients, although a short excitement phase during induction was noted in about 25 per cent of patients. Induction to the stage of respiratory depression seemed slower than with halothane, and of about the same duration as with methoxyflurane.

Once the tissues approached saturation, this state requiring about 30 to 40 minutes, muscular relaxation was adequate for intra-abdominal procedures. Frequently, as with halothane, the surgical incision produced movement of the patient, even though anesthesia was judged to be sufficient.

The electroencephalogram was not of assistance in determining stages and planes of anesthesia. Rapid, fast activity was predominant in surgical anesthesia, with or without adequate muscular relaxation. Occasionally, high voltage slow wave activity was superimposed on the fast activity (fig. 1). In only 2 patients was evidence of burst suppression activity seen.

Halopropane was a depressant to respiration of the same order as halothane and methoxyflurane. Like these drugs, manual control of respiratory exchange was accomplished easily. Surgical planes of anesthesia required assistance or control of ventilation in order to prevent respiratory acidosis.

In the absence of arrhythmias, pulse rate changes during the anesthetic course were not remarkable. Severe bradycardia was not seen, nor was tachycardia notable.

Reductions in arterial systolic blood pressure greater than 20 mm. of mercury occurred in 44 per cent of patients. In 12 per cent the reduction was greater than 20 mm. of mercury and in 14 per cent the blood pressure fell more than 40 mm. of mercury. For the most part, hypotension was noted during induction and before the surgical incision was made. Frequently the stimulus of incision produced an increase in blood pressure. Hypotension did not seem to develop as rapidly as in certain patients anesthetized with halothane, and it was associated with administration of high concentrations of the drug and the employment of controlled respiration.

Of particular significance during halopropane anesthesia was the incidence of cardiac arrhythmias; in view of the observations in dogs, these were perhaps to be expected (table

TABLE 2. Cardiac Arrhythmias during Halopropane Anesthesia.

	Patients	Percentage
No arrhythmias	36	44
Nodal rhythm	14	17
Significant arrhythmias	32	39

Incidence of cardiac arrhythmias in patients receiving halopropane.

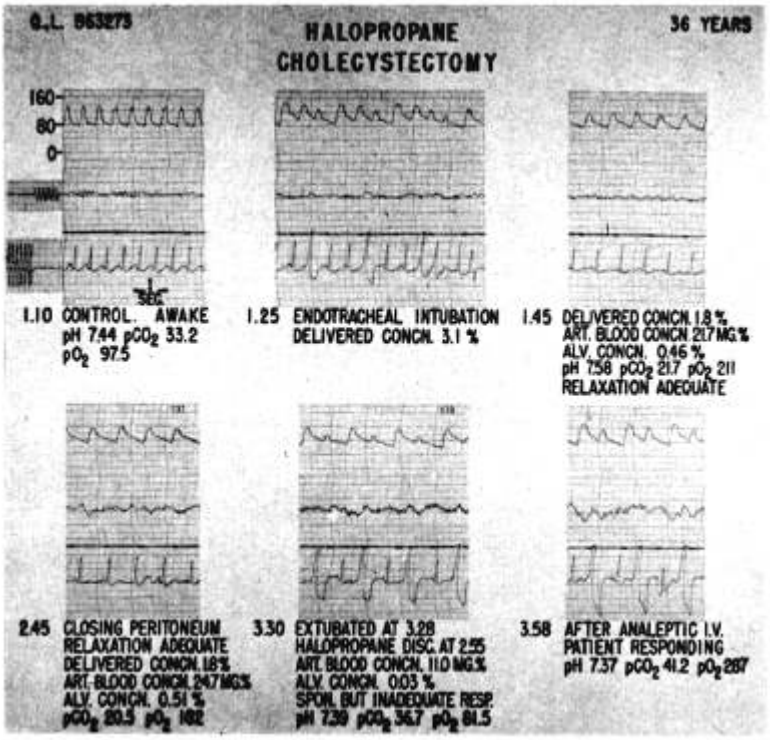

FIG. 2. From above downward in each tracing: arterial blood pressure, electroencephalogram, electrocardiogram. Note arrhythmias during induction and during emergence, and when acid-base balance was normal.

2). In this series, significant arrhythmias were noted in 39 per cent of the patients: these consisted of auricular and ventricular premature systoles, combinations of these, runs of ventricular tachycardia, and bizarre rhythms which were difficult to interpret (figs. 2 and 3). Most commonly the arrhythmias began as a bigeminy; in some instances it would disappear spontaneously, and in others it would progress to more worrisome patterns indicative of multifocal ventricular extrasystoles. On two occasions progressive irritability was such that the drug was discontinued. In one patient, a 64 year old woman with hypertension, who was undergoing operation for resection of an abdominal aortic aneurysm, ventricular tachycardia followed by ventricular fibrillation developed after the aortic clamp had been in place for 75 minutes. After 20 minutes of closed chest cardiac compression, administration of whole blood, rapid intravenous digitalization, and one application of the external defibrillator, spontaneous cardiac activity returned, and blood pressure rose to a satisfactory level. Aortic grafting was completed and the patient appeared to be convalescing satisfactorily when, on the third day postoperatively, she developed sudden cardiovascular collapse and died.

Complete recovery from anesthesia usually required from 1 to 2 hours following the operative procedure, even though halopropane was discontinued 30 to 45 minutes prior to the termination of operation. On return to the recovery room the pharyngeal and laryngeal reflexes would be present, the patient would respond to painful stimuli, but when left alone he would sleep. In this respect halopropane resembled methoxyflurane. That this prolongation of effect could be due to the selective storage of the anesthetic in the fatty tissues, with slow release from these depots when the drug was discontinued, was substantiated by the alveolar and arterial blood concentrations of halopropane (fig. 4). The readings to the left side of the graph were made approximately one hour after induction, at a time when the patient had reached a clinical stage of saturation. The readings to the right on the graph were made as the operation proceeded, and as the administered concentration of anesthetic was being reduced. The readings to the ex-

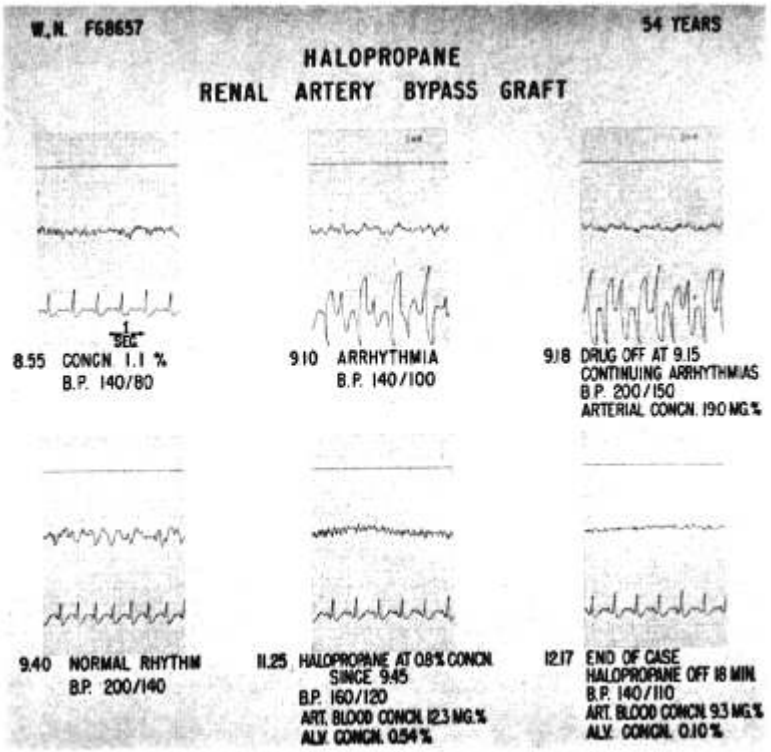

FIG. 3. Note severe cardiac arrhythmias which necessitated discontinuance of halopropane.

treme right were made at the conclusion of operation, when the halopropane had been discontinued for 30 to 45 minutes. Both the high affinity of halopropane for fatty tissues and its relatively high solubility in blood could account for the discrepancy at the end of operation between alveolar concentration and arterial blood content.

Discussion

Any new fluorinated compound must perforce stand favorable comparison with halothane and methoxyflurane. With regard to rapidity of induction, production of muscular relaxation, reversibility during maintenance, and prolongation of anesthetic effect postoperatively, halopropane can be placed between these two drugs, but lying closer on the scale to methoxyflurane. This intermediate position one might expect from the chemical and physical properties of the three drugs.

Of serious import in the usage of halopropane was the relatively high incidence of cardiac arrhythmias. Nodal rhythm may develop upon exposure to all potent anesthetic drugs, but with halopropane the frequent occurrence of bigeminal rhythm, auricular and ventricular extrasystoles, and multifocal ventricular tachycardia denotes a degree of cardiac irritability which cannot be ignored. In this series, the onset of arrhythmias did not appear to be directly related to increasing concentrations of halopropane in the blood stream. Rather, the cardiac irregularities were noted most frequently before the patient was clinically "saturated," and towards the conclusion of anesthesia. Often, increasing the depth of anesthesia brought about spontaneous cessation of the arrhythmias. The situation is reminiscent of the observation credited to Guedel that cyclopropane arrhythmias could be abolished by deepening the plane of anesthesia. However, in this instance the zone of irritability, if there be such, was in lighter planes of anesthesia.

In a number of patients the cardiac arrhythmias were precipitated, or made more serious, by factors such as insertion of an oral airway, administration of succinylcholine, or insertion of an endotracheal tube. In two patients ven-

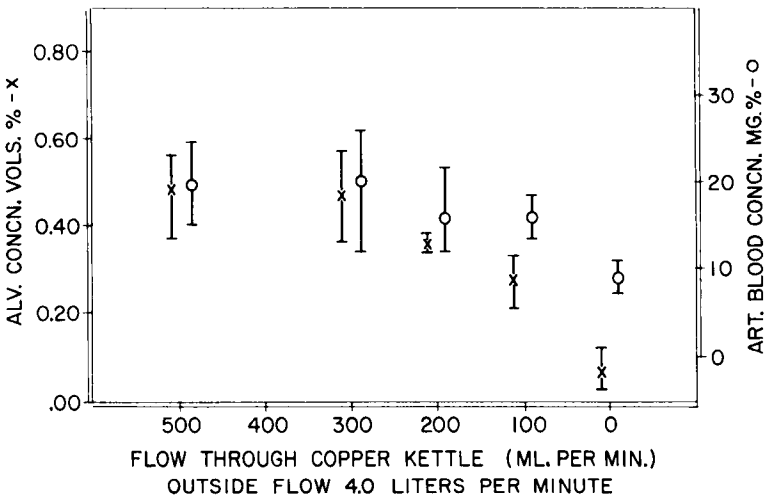

FIG. 4. Graph showing retention of halopropane in arterial blood with progressive reductions in alveolar concentrations.

tricular arrhythmias followed the administration of oxyphenonium, an anticholinergic drug similar to atropine. As Jones *et al.* pointed out, it is possible that the arrhythmias were precipitated, as in the case of cyclopropane, by vagal blockade in a heart already subject to strong sympathetic stimulation.[5]

The effect of hypercapnia in triggering arrhythmias is well known, and this may have initiated some of the irregularities seen. However, in those patients in whom blood gas measurements were made, respiratory acidosis was not present at the time arrhythmias developed (fig. 2). It is conceivable that the degree of hypercapnia required to produce arrhythmias under halopropane is not great, probably less than with halothane anesthesia.[5]

Arrhythmias are more prone to occur in older patients with arteriosclerotic heart disease. In this series, in which the average age was 40 years, the average age of patients in whom significant arrhythmias occurred was 47 years, whereas the average age of those showing no arrhythmia or only nodal rhythm was 35. It is possible that a relative myocardial ischemia contributed to the development of arrhythmias.

Cardiac irregularities sometimes follow certain types of surgical stimulation, such as exploration of the abdomen. In the group studied, the distribution of operative procedures was not significantly different in the patients whose cardiac rhythm was stable and in those who developed arrhythmias.

In conclusion, we do not believe that halopropane offers any advantages over the inhalation anesthetics used at present. It has the disadvantage of initiating, or allowing the precipitation of, cardiac arrhythmias in a fair proportion of patients to whom it is administered.

Summary

In dogs challenged with epinephrine under halopropane anesthesia, a high degree of myocardial irritability was found, with production of ventricular fibrillation at low challenging doses.

Halopropane was evaluated as an anesthetic in 82 patients. Induction concentrations ranged betweeen 3.4 and 3.9 volumes per cent, with maintenance concentrations between 0.4 and 1.8 volumes per cent. Arterial blood concentrations during anesthesia varied between 12 and 26 mg. per cent, with an average between 16 and 20 mg. per cent during maintenance.

Halopropane may be placed between halothane and methoxyflurane, but closer to methoxyflurane, in its effects on man. Induction was relatively slow, respiratory depression was marked as surgical planes of anesthesia were reached, and complete recovery was delayed for 1 to 2 hours following termination of anesthesia. An explanation for delayed recovery was found in the persistence of relatively high arterial blood content of drug at the end of

anesthesia, at a time when the alveolar concentration was low.

The greatest drawback to halopropane was the incidence of significant cardiac arrhythmias, noted in 39 per cent of patients. Evidence suggests that this drug sensitized the myocardium to the effects of sympathetic stimulation.

Halopropane is not recommended for clinical use at this time.

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Nothing New Under the Sun

From the *American Journal of the Medical Sciences,* New Series, Vol. 24, 1852, p. 272.

Morphine and Chloroform. The following are extracts from a London newspaper, *The Atlas,* April 10, 1852; and are, therefore, not as good authority as a medical journal, but still they may be correct in all respects:

"A physician in Prague has just died a real 'martyr to science.' He had been in the habit of taking strong doses of poison, after swallowing an antidote, in order to note their effects. On the 23d ult., he took so large a quantity of morphine, that all the efforts of some medical friends present at the exhibition could not save him.

"In resuscitating from an overdose of chloroform, galvanism is the only chance. Keep up a current of electricity through the fifth nerve, medulla oblongata, phrenic nerves, and diaphragm, as long as respiratory movements can be produced, and let the patient have plenty of fresh air or oxygen gas, and the case must do well, for the blood must remain fluid for a long time, and circulation will go on as long as respiration continues to go on artificially. The blood and the air-cells throw off their load, and in proportion as the pneumogastric, medulla oblongata, and motor nerves, slowly resume their functions, so respiration begins to assume a less artificial character; at length, the cerebrum aids us, and respiratory movements, both voluntary and involuntary, keep up the functions of life unaided."

Dr. Hercpath.