Halopropane Anesthesia in Man

Laboratory and Clinical Studies

Robert W. Virtue, M.D., Richard V. Young, M.D., Lawrence O. Lund, M.D., John H. K. Vogel, M.D., Robert F. Grover, M.D.

In recent years an interesting group of fluorinated compounds has been introduced to anesthesiology. The addition of fluorine to hydrocarbons diminishes flammability as do other halogen atoms. Since fluorine has a lower atomic weight than chlorine or bromine, the volatility of fluorinated compounds is more likely to render them useful as inhalation anesthetic agents. A new compound in this group, 1,1,2,2-tetrafluoro-3-bromo-propane (halopropane) has become available for evaluation. It is a colorless liquid with molecular weight of 195. The specific gravity is 1.81 at 20° C. and 1.805 at 25° C.; the index of refraction n_D^{25} is 1.3358; vapor pressure in mm. of mercury is 88 at 20°, 113 at 25°, 145 at 30°, and 181 at 35° C.; heat of vaporization is 43 calories per gram. Approximately 0.4 grams of halopropane are soluble in 100 grams of water. The blood/gas partition coefficient is 5.8, the oil/gas ratio 323 and the oil/water distribution coefficient is 130.[1] The vapor is nonflammable in oxygen with an instantaneous spark at 10 joules and with a hot wire at 950°. Breakdown could not be detected on exposure to soda lime, or with 10 per cent NaOH at 80° C. The compound was not decomposed during 20 hours exposure to a 275-watt sun lamp. The liquid has a pleasant odor and is nonirritating to the respiratory tract.

Preliminary evaluation of halopropane has been carried out at the Haskell Laboratory and by Fabian and his co-workers.[2] The former anesthetized eight dogs for two hours for five consecutive days. Microscopic sections of lung, spleen, pancreas, adrenal glands, kidneys, spinal cord, bone marrow and liver showed no pathologic changes. Fabian's group studied the effects of halopropane in 56 unpremedicated dogs. Bromsulphalein retention was determined in 15. Only one animal had more than 5 per cent retention in twenty-four hours. Both depolarizing and nondepolarizing relaxing agents afforded satisfactory muscle relaxation without change in blood pressure. Methoxamine and phenylephrine increased the blood pressure without production of arrhythmias. Ephedrine and desoxyephedrine each produced premature ventricular systoles. Epinephrine and norepinephrine caused ventricular fibrillation.

Eight of the 56 dogs were given halopropane for three to four hours on each of six consecutive days. They were killed with an overdose (10 per cent) of halopropane. Studies of the fixed tissues revealed no pathologic changes.

Bronchospasm was absent during induction. The pulse rate usually increased moderately. Arrhythmias occurred in 24 per cent of the animals; most were nodal rhythms; 5 per cent were bigeminal rhythms which disappeared with artificial ventilation. Hypotension occurred during deep anesthesia, but the blood pressure was close to normal in light surgical anesthesia. The contractile force of the heart determined with a Walton-Brodie strain gauge was lowered approximately 15 to 20 per cent in light anesthesia, and as much as 50 per cent in deep anesthesia. Evidence of intercostal weakening was seen when the EEG depth was stage III. Respiratory arrest occurred with 7 per cent halopropane. Adequate surgical anesthesia was obtained at 1.5 per cent concentration.

After obtaining the above data, Fabian and associates[3] successfully administered halopro-

Received from the Division of Anesthesiology and Cardiovascular Pulmonary Laboratory, University of Colorado Medical Center, Denver, Colorado; accepted for publication December 12, 1962. This work was done while Dr. Vogel was under the tenure of a postdoctoral fellowship, National Heart Institute, United States Public Health Service, Bethesda, Maryland.

pane to more than two hundred patients undergoing operation. After consultation with these workers, we administered halopropane to normal healthy volunteers to determine its effect on the respiratory and cardiovascular systems. Its effectiveness as an anesthetic agent in the operating room was then observed.

Methods

Eight healthy young male volunteers ranging from 21 to 29 years of age were anesthetized with halopropane without surgical intervention. After a 16-hour fast, each subject received 0.4 mg. of scopolamine hydrobromide intravenously. ECG leads were attached. A no. 18 Cournand needle was placed in the brachial artery, and a length of polyethylene 90 tubing was introduced proximally through an antecubital vein. Respiratory rate, tidal volume, blood pressure and pulse were measured. Sufficient practice was done in measuring normal ventilation so that a reproducible minute volume could be obtained. Cardiac output was measured in duplicate by the indicator-dilution technique using indocyanine green. Arterial pressure was recorded directly via the brachial artery.

The subjects were then allowed to breathe increasing concentrations of halopropane and oxygen from a closed circle absorption system until sufficiently anesthetized for endotracheal intubation. The agent was vaporized in a Foregger copper kettle. No relaxant or other anesthetic was used. Electroencephalographic leads were attached as soon as unconsciousness had been attained. Halopropane in concentrations up to 6 per cent was utilized for induction. Following tracheal intubation, halopropane was volatilized with air in a nonrebreathing system with the subjects breathing spontaneously. The concentration of halopropane was regulated so that an EEG level of burst suppression was barely attained; this required approximately 2 per cent halopropane (equal to 1.7 per cent at sea level), as calculated from the vapor pressure and flow meters. When burst suppression first appeared, measurements of ventilation, blood pressure, pulse and cardiac output were made. The anesthetic gas flow was maintained thereafter at this concentration. Upon completion of the measurements, controlled respiration was begun, maintaining minute volume at the control level with a mechanical respirator, and using a larger tidal volume and slower rate than the patient had practiced spontaneously. When a steady state of blood pressure, pulse and EEG had been reached and maintained for twenty minutes, measurements were repeated. Finally, the lungs were hyperventilated for about twenty minutes to eliminate the drug and the subjects were allowed to awaken.

The effects of halopropane anesthesia on hepatic and renal function were determined in twelve patients scheduled for operation. Control preoperative measurements were made of Bromsulphalein (BSP) retention,[3] bleeding time,[4] clotting time,[5] blood glucose,[6] blood volume,[7, 8] blood urea and urea clearance[9] on the day before operation. The patients were given premedication, generally with 100 mg. meperidine and 0.4 mg. 70 kg. of scopolamine, subcutaneously one and one-half hours before anesthesia. Induction was carried out with thiopental intravenously, followed by 40 mg. of succinylcholine intravenously for tracheal intubation. A flow of 500 ml. each of nitrous oxide and oxygen was used, and halopropane was added to maintain surgical anesthesia. For one hour before operation halopropane was given and respiration assisted to maintain adequate tidal exchange; blood volume, hematocrit, glucose, *p*H, carbon dioxide, and urea determinations were then repeated. Determinations of arterial *p*H and carbon dioxide were made about two hours postoperatively. Electrocardiograms were recorded intermittently throughout. Bromsulphalein retention and urea clearance were also determined the next day.

Thirty additional patients were anesthetized with this drug during operation. Electrocardiographic determinations were made, but no blood constituents were measured.

Results

Duplicate determinations of cardiac output were in close agreement. Table 1 indicates that cardiac output was not significantly altered from normal during halopropane anesthesia in the volunteer subjects. The appearance time of the dye was significantly shorter when halopropane was used. In addition, the

TABLE 1. Halopropane Anesthesia (Eight Volunteers

	Cardiac Output liters/minute			Systolic Blood Pressure mm. Hg			Venous Pressure cmm. Hg			Pulse beats/minute		
	C	S	A	C	S	A	C	S	A	C	S	A
Range	4.8–7.4	6.1–9.9	4.3–8.6	100–136	64–110	60–100	6–8	6–18	5–9.5	57–92	80–100	80–109
Mean	5.91	6.74	5.91	118	92	84	6.9	8.9	7.7	73	93	96
Std. Dev.	1.0	1.7	1.1	12.4	13.7	13.8	1.1	3.9	1.8	12	7.2	13.0
SE±	.39	.63	.52	4.7	5.2	5.2	.45	1.5	.68	4.5	2.7	4.9
	N.S.	N.S.	N.S.				N.S.	N.S.	N.S.			
				C S, C A, P = .001 S A, N.S.						C S, C A, P = .001 S A, N.S.		

	Dye Appearance Time seconds			Peripheral Resistance			Oxygen Uptake c.c./minute			Carbon Dioxide Output c.c./minute		
	C	S	A	C	S	A	C	S	A	C	S	A
Range	6.5–13.4	5.5–7.4	5.8–8.4	708–1,407	396–832	561–1,100	200–276	154–424	147–366	149–190	94–236	136–318
Mean	9.90	6.20	6.69	1,100	701	775	242	264	246	172	160	210
Std. Dev.	2.52	.68	.80	249	152	208	31.7	93.0	78.5	16.1	61.7	60.1
SE±	.88	.26	.34	94	58	85	11.2	41.6	35.1	7.2	27.6	27.0
							N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
	C A, C S, P = .001 S A, N.S.			C S, P = .001 S A, N.S. C A, P = .01								

	Minute Volume liters			Elapsed Times	Minutes	
	C	S	A		Range	Average
Range	4.31–6.95	5.2–6.11	4.85–8.58	Start to Intubation	0–52	32
Mean	5.46	5.54	6.11	Time before cardiac output on spontaneous respiration	42–80	61
Std. Dev.	1.11	.29	1.31	Time between determinations on spontaneous and controlled respiration	20–65	29
SE±	.43	.11	.53	Time from last determination until recovery	130–247	200
	N.S.	N.S.	N.S.			

C = Control, S = Spontaneous Breathing, A = Artificial Ventilation.

blood pressure was lower than normal whether ventilation was spontaneous or assisted. The pulse rate increased and the calculated peripheral resistance decreased. Ventilation, when spontaneous, became rapid and shallow, but with no change in minute volume. There was a tendency for less carbon dioxide to be eliminated and for blood *p*H to fall. Premature ventricular contractions and episodes of bigeminy were frequent during spontaneous ventilation. When intermittent positive-pressure breathing was begun with an increased tidal volume, the alveolar ventilation improved, even though the minute volume remained nearly identical and carbon dioxide elimination was increased. This also resulted in disappearance of the arrhythmias. Blood pressure remained diminished so long as the inhaled concentration of halopropane was constant. Waking was slow. The subjects remained lethargic for at least three hours after anesthesia, even though a twenty-minute period of hyperventilation had been used to eliminate the anesthetic drug.

Table 2 shows the blood volume, blood glucose, blood urea, and bleeding and clotting times in the surgical patients. The only differences before and after halopropane were the slightly lower *p*H values obtained postoperatively. The depth of halopropane anesthesia was less than that obtained in the volunteer group.

The remaining thirty patients who received halopropane had no untoward effects, unless the abnormal electrocardiograms of two are included in this category. Anesthesia was smooth, and prolonged waking periods were avoided by discontinuing anesthesia thirty minutes prior to the end of operation. Nitrous oxide perhaps enabled operation to proceed with less halopropane than when used with oxygen alone. Depth of anesthesia was com-

TABLE 2. Halopropane-Nitrous Oxide Anesthesia (Twelve Surgical Patients)

	Blood Volume (ml.)		Hematocrit (%)		Glucose (mg./100 ml.)		pH			Arterial Carbon Dioxide (vol. %)		
	Control	1 Hour	Control	1 Hour	Control	1 Hour	Control	1 Hour	Rec. Room	Control	1 Hour	Rec. Room
Range	3,312–5,050	3,300–4,800	32–48	33–46	55–185	59–220	7.38–7.59	7.36–7.59	7.36–7.48	28.8–49.7	26.2–46.2	32.2–46.0
Mean	4,175	4,025	40.36	40.67	103	118	7.45	7.44	7.41	40.1	38.4	38.5
Std. Dev.	550	492	5.06	4.6	35	54	.05	.08	.04	5.2	5.2	4.4
SE	166	148	1.52	1.40	11	17	.01	.025	.01	1.6	1.9	1.7
							N.S.	N.S.				
							P = .05					

	BSP Retention (mg./100 ml.)		Urea N (mg./100 ml.)		Urea Clearance (ml./minute)		Bleeding Time (seconds)		Clotting Time (minutes)	
	Control	Postop.	Control	1 Hour	Control	Postop.	Control	Postop.	Control	Postop.
Range	0–18	0–26	5–18	4–39	14 4,000 cc. max.	10–219	75–150	70–180	5–10	6.5–12
Mean	4	10	9.7	10.6	29	48	118	136	7.5	8.6
Std. Dev.	6.8	8.3	3.6	4.7	19.7	56.7	23	27	1.3	1.7
SE	2.1	2.7	1.1	1.5	7.0	17.9	8	9	.4	.5

The only statistically significant difference

paratively superficial and recovery time was a fraction of that required when halopropane alone was administered to the volunteers.

Discussion

Halopropane is similar to halothane [10] and methoxyflurane [11] in that it tends to lower blood pressure and reduce effective ventilation when deeper levels of anesthesia are reached. At depths adequate for surgical anesthesia, cardiac output is maintained at control levels, as found for halothane and Fluoromar,[12] although some have reported a decreased cardiac output with halothane, and others, both decreased and unchanged at elevated values.[13, 14]

Consistent changes in blood, hepatic, or renal function during anesthesia with halopropane uncomplicated by operation were not found in these twelve surgical patients. The average blood sugar was elevated 13 per cent. BSP retention showed a slight twenty-four elevation, but no more than expected after similar operations performed with other anesthetics. There were no significant differences in bleeding or clotting time after one hour of anesthesia. Urea clearance and urea nitrogen were both within normal range following operation. Blood volume and hematocrits were unchanged suggesting no alteration of vascular capillary permeability. pH and arterial P_{CO_2} remained normal during the hour of anesthesia.

Induction of anesthesia in the volunteers was relatively slow, as expected from the comparatively high blood solubility of halopropane. Waking was even slower. Again this was predictable from the high fat and blood solubility coefficients. Methoxyflurane is the only agent known to have a greater fat solubility, oil/gas ratio = 825.* Chenoweth [15] recorded significant concentrations of methoxyflurane in fat forty hours after anesthesia.

In the thirty additional surgical patients spontaneous pulmonary ventilation was lessened with halopropane. This probably resulted in retention of carbon dioxide, which may explain the cardiac arrhythmias. At the end of one operation, bigeminal rhythm appeared one minute after the patient was permitted to breathe spontaneously. Measurement of tidal volume showed it to be 135 ml.; the dead space was estimated to be 150 ml. Ventilation was then assisted until more agent and carbon dioxide were eliminated and the patient's tidal volume reached 250 ml.; cardiac rhythm became regular. Extubation was performed and the patient was again permitted to breathe spontaneously; bigeminal rhythm returned. Intermittent positive pressure with a bag and mask was used until the spontaneous tidal volume reached 375 ml. The rhythm then became and remained regular. In a few other patients bigeminal rhythm occurred when ventilation was permitted to become spontaneous, a circumstance reminiscent of the early days of cyclopropane anesthesia.

* Eger, E. I.: personal communication.

As implied, with adequate pulmonary ventilation, halopropane could be used safely. When used with nitrous oxide the blood pressure drops were not significant. In some cases when nitrous oxide was an adjuvant, only low concentrations of halopropane were required, and respiration increased so that the impression was gained that halopropane seemed to be a respiratory stimulant. The drug acts entirely too slowly for application without some other induction agent. It appears to have excellent analgesic qualities, for the surgeon may make an incision while the patient is still "light," and elicit no untoward response. This is in contrast to halothane.[16]

Summary

Halopropane was administered to eight volunteers without supplemental agents. Cardiac output, venous pressure, oxygen uptake, carbon dioxide output, and respiratory minute volume revealed no significant changes whether the subjects breathed spontaneously or were artificially ventilated. Blood pressure was consistently diminished under these circumstances. During spontaneous ventilation tidal volume decreased and bigeminal rhythms were frequent; these cleared with assisted ventilation. Induction time was impractically long, and recovery time of considerable duration.

Twelve surgical patients were anesthetized for one hour before operation with halopropane and 50 per cent nitrous oxide after thiopental induction. Blood volume, hematocrit, blood glucose, blood urea, blood carbon dioxide, bleeding and clotting times were unaltered as were BSP retention and urea clearance the following day.

Electrocardiograms made on 30 additional subjects undergoing halopropane-nitrous oxide anesthesia with assisted ventilation were virtually all within normal limits. With adequate ventilation, therefore, halopropane was a useful anesthetic in operations of reasonable duration.

Support for this work was supplied by the Organic Chemical Division, du Pont de Nemours Company, Wilmington, Delaware.

References

1. Merkel, G., and Eger, E. I.: A comparative study of halothane and halopropane anesthesia in dogs, ANESTHESIOLOGY, In press.
2. Fabian, L. W., Gee, H. L., Dowdy, E. G., Dunn, R. E., and Carnes, M. A.: Laboratory and clinical investigation of a new fluorinated anesthetic compound, $CHF_2CF_2CH_2Br$ (halopropane®), Anesth. Analg. **41**: 707, 1962.
3. Rosenthal, S. M., and White, E. C.: Clinical application of Bromsulphalein test for hepatic function, J. A. M. A. **84**: 1112, 1925.
4. Duke, W. W.: Relation of blood platelets to hemorrhagic disease, J. A. M. A. **55**: 1185, 1910.
5. Lee, R. I., and White, P. D.: Clinical study of coagulation time of blood, Amer. J. Med. Sci. **145**: 495, 1913.
6. Nelson, N.: Photometric adaption of Somogyi method for determination of glucose, J. Biol. Chem. **153**: 375, 1944.
7. Crispell, K. R., Porter, B., and Nieset, R. T.: Studies of plasma volume using human serum albumin tagged with radioactive iodine, J. Clin. Invest. **29**: 513, 1950.
8. Storaasli, J. P., Krieger, H., Friedell, H. L., and Holden, W. D.: Use of radioactive iodinated plasma protein in study of blood volume, Surg. Gynec. Obstet. **91**: 438, 1950.
9. Karr, W. G.: Method for determination of blood urea nitrogen, J. Lab. Clin. Med. **9**: 329, 1924.
10. Stephen, C. R., and Little, D. M.: Halothane, Baltimore, Williams & Wilkins Co., 1961, p. 40.
11. Wasmuth, C. E., Greig, J. H., Heni, J., Moraca, P. P., Isil, N. H., Bitts, E. M., and Hale, D. E.: Methoxyflurane a new anesthetic agent, Cleveland Clin. Quart. **27**: 174, 1960; Bagwell, M. S., and Woods, E. F.: Cardiovascular effects of methoxyflurane, ANESTHESIOLOGY **23**: 31, 1962.
12. Virtue, R. W., Vogel, J. H. K., Press, P., and Grover, R. F.: Respiratory and hemodynamic measurements during anesthesia. Use of trifluoroethyl vinyl ether and halothane, J. A. M. A. **179**: 224, 1962.
13. McGregor, M., Davenport, M. T., Jegier, W., Seklj, P., Gibbons, J. E., and Demers, P. B.: Cardiovascular effects of halothane in normal children, Brit. J. Anaesth. **30**: 398, 1958.
14. Wyant, G. M., Merriman, J. E., Kilduff, C. J., and Thomas, E. T.: The cardiovascular effects of halothane, Canad. Anaesth. Soc. J. **5**: 384, 1958.
15. Chenoweth, M. B., Robertson, D. N., Erley, D. S., and Gollhke, R.: Blood and tissue levels of ether, chloroform, halothane and methoxyflurane in dogs, ANESTHESIOLOGY **23**: 101, 1962.
16. Hampton, L. J., and Flickinger, H.: Closed circuit anesthesia utilizing known increments of halothane, ANESTHESIOLOGY **22**: 413, 1961.