COMPARISON OF THE CARDIOVASCULAR, RESPIRATORY AND METABOLIC EFFECTS OF METHOXYFLURANE AND HALOTHANE IN DOGS

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METHOXYFLURANE (Penthrane) has been offered for evaluation as a new inhalation anesthetic agent. Preliminary studies of this agent suggested that it had several properties which might place it above presently available inhalation agents.

It has great potency within the therapeutic range so that no supplement is needed to acquire surgical anesthesia. Prolonged analgesia and amnesia occur so that the need for postoperative narcotic analgesics seems to be reduced. There is little or no irritant effect on the myocardium, so that arrhythmias due to anesthesia do not occur.[1, 2] Although first reports stated that there is no sensitization of the heart to epinephrine, this has now been shown to be false.[3] Good muscle relaxation is observed during surgical anesthesia. In addition, methoxyflurane is nonexplosive, and has a stable molecule which is unaffected by exposure to the carbon dioxide absorbents, but it is affected by light (due possibly to the addition of dibenzylamine to prevent acid breakdown products) and should be stored in dark bottles.[4]

The various attributes of methoxyflurane have been observed by others, but clinical experience with this agent is still limited. Some of its anesthetic properties appear to be similar to those of chloroform and halothane. Since halothane is now being used widely, it was chosen as the counterpart in a comparative study in dogs.

METHOD

On the basis of preliminary trial, methoxyflurane appeared to us to have approximately twice the hypnotic potency of halothane, so one per cent methoxyflurane was compared to two per cent halothane. These concentrations were the least which were just sufficient to allow a stable level of anesthesia without the animal reacting to the endotracheal tube during maintenance of anesthesia.

Studies were performed on 18 medium-sized mongrel dogs weighing 10.7 to 23.2 kg. (mean 15.7 kg.). One agent was administered for 90 minutes, and then, after a period of recovery sufficient to permit the dogs to react to the endotracheal tube, the other agent was used for a consecutive 90 minute period. Oxygen was administered between the anesthetic agents, but no attempt was made to eliminate completely the previous agent before the experiment was resumed with the second agent. Three weeks later the procedure was repeated, but the order of administration was reversed. In six of the dogs, spontaneous breathing was allowed throughout all the experiments (except when apnea ensued), while in the other twelve dogs, breathing was augmented throughout each experiment with a Takaoka respirator. Augmented breathing was accomplished by delivering a flow of oxygen through the vaporizer and to the Takaoka respirator which would provide approximately the same minute volume of breathing as was observed prior to administration of anesthesia. Although it was recognized that the dogs whose breathing was augmented might receive a higher alveolar and blood level of the anesthetic vapors than those breathing spontaneously, no attempt was made to regulate other than the inhaled concentration.

Each dog was premedicated with 5 mg. perphenazine (Trilafon) intramuscularly one hour before an experiment. Light anesthesia was induced with a 'sleep' dose of thiopental (75 to 150 mg.) and the animal's trachea was intubated. Oxygen was given through a calibrated Fluotec vaporizer when halothane was in use, and through a Chlorotec vaporizer previously calibrated with methoxyflurane, when the latter was used. A nonrebreathing circuit

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TABLE 1

SUMMARY OF SOME METABOLIC EFFECTS OF 2 PER CENT HALOTHANE AND 1 PER CENT METHOXYFLURANE IN DOGS BREATHING SPONTANEOUSLY

Parameters*	Control	2 Per Cent Halothane, 90 Minutes	1 Per Cent Methoxyflurane, 90 Minutes	Control	1 Per Cent Methoxyflurane, 90 Minutes	2 Per Cent Halothane, 90 Minutes
*p*H	7.20	7.10	7.08	7.24	7.16	7.04
S.D.	0.06	0.09	0.07	0.09	0.11	0.18
Total CO_2, m*M*/l.	24.5	27.5	28	25.5	27.0	28.0
S.D.	1.5	6.9	1.8	1.6	2.6	2.0
P_{CO_2}, mm. Hg	61	85	90	59	73	100
S.D.	6.8	22.4	15.4	8.6	15.9	41.5
HCO_3^-, m*M*/l.	22.5	25	25.5	23.5	25	25
O_2, % Saturation	93	94	96	98	97	97
S.D.	4.5	6.7	3.5	2.4	2.8	2.5
Hematocrit	36	34	34	37	35	34
S.D.	4.1	4.0	3.8	4.0	4.4	5.3
Potassium, mEq./l.	3.6	4.2	4.2	3.8	4.5	4.7
S.D.	0.24	0.42	0.45	0.23	0.48	0.89
Sodium, mEq./l.	154	153	152	152	158	155
S.D.	5.7	3.2	3.9	2.3	6.6	4.2
Chloride, mEq./l.	113	114	115	116	114	115
S.D.	0.9	1.8	4.6	3.4	4.5	3.5
Glucose, mg.%	96	95	89	95	84	90
S.D.	11.8	4.7	8.3	7.9	6.4	10.9
CCF† Control	0	0	0	0	0	0
24 hour	2.5	3.5	3	2.5	3.5	3.5
48 hour	2.5	3	2.5	2	2.5	2.5

* Each value is the mean of 6 determinations.
† Cephalin cholesterol flocculation.
S.D. = standard deviation.

was used in all experiments, employing a non-return valve when breathing was spontaneous. The Takaoka respirator vents expired gas to the air, so that no non-return valve was required when breathing was augmented.

The anesthetic agent under test initially was not administered until the monitoring equipment was set up, readings were recorded and blood samples drawn for 'control' determinations. Sufficient time was permitted to elapse so that the thiopental administered would not affect significantly the physiological parameters being measured.

Anaerobic arterial blood samples and venous blood samples were drawn at the beginning of each experiment and at the end of the administration of each of the two anesthetics. These were analyzed by standard laboratory techniques to determine the arterial *p*H (Beckman G S *p*H meter), total CO_2 (modified Van-Slyke manometric method), plasma sodium and potassium (method with flame photometer), oxygen saturation (D U spectrophotometer), hematocrit [5] (Natelson micromethod), chloride [6] (Schales and Schales method), blood glucose [7] (Folin and Wu method) and cephalin cholesterol flocculation [8] (Hanger method).

Arterial and venous blood pressures were recorded through cannulas inserted through the femoral vessels into the aorta and inferior vena cava and attached to Statham strain gauges. A Wright respirometer was interposed between the endotracheal tube and the nonrebreathing valve or Takaoka respirator, to

record the minute volume. Gas flow in the airway was recorded with a pneumotachygraph via a needle inserted into the lumen of the endotracheal tube for the purpose of recording the rate of respiration. Lead 2 of the electrocardiogram, blood pressures and the gas flow curves were recorded simultaneously and continuously throughout all the experiments on a Grass polygraph ink recorder.

Serial cardiac output estimations were made at the same intervals as blood samples were drawn, using radioactive iodinated human serum albumin injections by a standardized technique which has been reported previously and has been shown to give reliable values.[9, 10, 11]

The data derived from the tracings of each experiment were tabulated and graphed in order to show the mean values at 10 minute intervals from the individual mean values over a representative 10 second strip of the recording. The cardiac output and chemical blood test data were analyzed at three intervals (control and 90 minutes of each anesthetic).

All data were reviewed statistically to determine whether the differences observed between the two agents were significant.

Results

Anion-Cation Balance. During spontaneous breathing the *p*H, plasma bicarbonate and P_{CO_2} in the arterial blood changed in the direction of progressive respiratory acidosis with both anesthetic agents. No significant

TABLE 2

Summary of Some Metabolic Effects of 2 Per Cent Halothane and 1 Per Cent Methoxyflurane in Dogs with Augmented Breathing

Parameters*	Control	2 Per Cent Halothane, 90 Minutes	1 Per Cent Methoxyflurane, 90 Minutes	Control	1 Per Cent Methoxyflurane, 90 Minutes	2 Per Cent Halothane, 90 Minutes
*p*H	7.32	7.35	7.30	7.35	7.35	7.27
S.D.	0.05	0.07	0.09	0.08	0.13	0.08
Total CO_2, m*M*/l.	22	22	22	22	22	22.5
S.D.	3.1	2.6	2.8	1.9	3.5	1.9
P_{CO_2}, mm. Hg	42	40	43	40	42	49
S.D.	7.8	7.5	12.2	11.2	17.0	12.3
HCO_3^-, m*M*/l.	20.5	21.0	20.5	21	20.5	21
O_2, % Saturation	97	97	96	94	96	95
S.D.	3.7	3.4	4.7	7.2	5.7	6.4
Hematocrit	36	35	36	36	35	35
S.D.	5.5	4.9	5.3	4.3	4.0	4.7
Potassium, mEq./l.	3.5	3.6	3.6	3.8	3.7	3.7
S.D.	0.16	0.21	2.4	1.02	0.5	0.55
Sodium, mEq./l.	153	153	151	155	153	152
S.D.	4.6	2.6	4.2	6.0	3.4	4.5
Chloride, mEq./l.	113	117	119	116	119	117
S.D.	3.1	3.0	3.1	4.8	3.7	3.5
Glucose, mg.%	95	88	75	93	81	79
S.D.	10.9	12.9	16.7	9.0	11.4	10.0
CCF† Control	0	0	0	0	0	0
24 hour	3	3	3	3.5	3	3
48 hour	2	2.5	2.5	2.5	2.5	2

* Each value is the mean of 12 determinations.
† Cephalin cholesterol flocculation.
S.D. = standard deviation.

alteration was observed when breathing was augmented. The mean values are shown in tables 1 and 2. The effect produced by the two agents was not significantly different, although methoxyflurane caused a slight trend toward metabolic acidosis, which was not observed with halothane.

Serum Electrolytes. During spontaneous breathing, the serum potassium rose during the administration of both methoxyflurane and halothane. The serum chloride and sodium did not change. When breathing was augmented none of these values changed (tables 1 and 2).

Blood Sugar and Cephalin Cholesterol Flocculation. There was no significant alteration in the blood sugar during anesthesia with either agent when breathing was spontaneous. When breathing was augmented, there was a slight trend to hypoglycemia with both agents. Cephalin cholesterol flocculation became positive during the administration of both agents regardless of whether breathing was spontaneous or augmented, but returned to control values in each case before the subsequent crossover experiment was carried out (tables 1 and 2).

Hematocrit Determination and Oxygen Saturation. There were no significant alterations evident from the estimations made in these regardless of whether breathing was spontaneous or augmented (tables 1 and 2).

Electrocardiogram. In the animals that were allowed to breathe spontaneously, the only obvious change was a moderate decrease in voltage. In a few instances, there was also a moderate to severe T-wave depression when respiratory efforts became very small and approached apnea. There were no disturbances in cardiac rhythm observed during methoxyflurane or halothane anesthesia when pulmonary ventilation was augmented.

Circulatory and Respiratory Effects. The mean values for the measured and derived vital signs during spontaneous breathing in 6 dogs and during augmented breathing in 12 dogs is shown in tables 3 and 4 respectively. The mean arterial blood pressures, pulse rates, tidal volume and rate of respiration are shown graphically in figures 1 and 2.

TABLE 3

SUMMARY OF THE HEMODYNAMIC AND RESPIRATORY EFFECTS OF 2 PER CENT HALOTHANE AND 1 PER CENT METHOXYFLURANE IN DOGS BREATHING SPONTANEOUSLY

	Halothane		Methoxyflurane		Methoxyflurane		Halothane	
	Control	90 Minutes	Control	90 Minutes	Control	90 Minutes	Control	90 Minutes
Systolic B. P., mm. Hg	153	102	145	122	145	117	138	105
S.D.	11.7	10.3	22.4	12.1	14.1	16.9	17.9	12.8
Diastolic B. P., mm. Hg	107	57	100	71	94	71	95	60
S.D.	14.7	5.2	22.4	8.6	9.7	13.9	15.0	6.2
Mean B. P., mm. Hg	122	72	116	88	111	86	109	75
Pulse pressure, mm. Hg	46	45	45	52	51	47	43	45
Venous pressure, mm. Hg	5	3	4	4	4	4	4	6
Pulse rate/minute	135	103	101	106	139	109	105	102
S.D.	31.8	3.9	14.7	13.9	44.0	14.5	20.1	12.4
Cardiac output (blood volumes/min.)	3.52	2.48		1.98	2.98	2.06		1.60
Resp. rate/minute	13	14	19	11	14	11	16	20
S.D.	7.4	11.9	11.2	9.1	8.8	7.7	15.1	16.7
Tidal Volume ml.	218	170	210	186	201	215	204	147
S.D.	63.2	44.1	61.6	59.4	63.4	72.4	69.4	33.1
Minute Volume, liters	2.83	2.38	3.99	2.05	2.81	2.37	3.26	2.94

TABLE 4

SUMMARY OF THE HEMODYNAMIC AND RESPIRATORY EFFECTS OF 2 PER CENT HALOTHANE AND 1 PER CENT METHOXYFLURANE IN DOGS WITH AUGMENTED BREATHING

	Halothane		Methoxyflurane		Methoxyflurane		Halothane	
	Control	90 Minutes	Control	90 Minutes	Control	90 Minutes	Control	90 Minutes
Systolic B. P., mm. Hg	150	116	137	98	142	90	108	96
S.D.	15.4	26.5	19.4	23.6	13.4	19.4	17.6	17.7
Diastolic B. P., mm. Hg	100	72	108	60	97	54	67	57
S.D.	32.4	19.8	36.4	14.1	12.5	16.7	18.0	15.1
Mean B. P., mm. Hg	124	87	106	73	112	66	80	70
S.D.								
Pulse Pressure mm. Hg	47	44	47	38	45	36	41	39
Venous Pressure, mm. Hg	3	3	3	4	4	5	5	5
Pulse Rate/minute	124	81	84	73	108	85	80	67
S.D.	35.3	31.0	36.4	16.9	18.1	21.8	17.8	17.5
Cardiac Output (blood volumes/min.)	2.55	2.33		2.79	3.24	2.60		2.44
Resp. Rate/minute	22	26	27	31	25	27	26	29
S.D.	4.9	3.4	4.0	3.1	4.2	4.0	4.3	4.0
Tidal Volume, ml.	184	157	171	144	194	154	161	150
S.D.	53.6	33.4	59.0	26.9	44.4	56.5	25.4	30.5
Minute Volume, liters	4.04	4.08	4.62	4.46	4.85	4.16	4.19	4.35

During spontaneous breathing, the trend to a decrease in the mean arterial blood pressure was greater with halothane than with methoxyflurane, although the difference was not large. Alterations in pulse pressure were not significant. Both agents caused slowing of the pulse rate. Cardiac output fell to a greater degree with halothane than with methoxyflurane. During augmented breathing the depressant effect on blood pressure, pulse rate and cardiac output were not significantly different with the two agents.

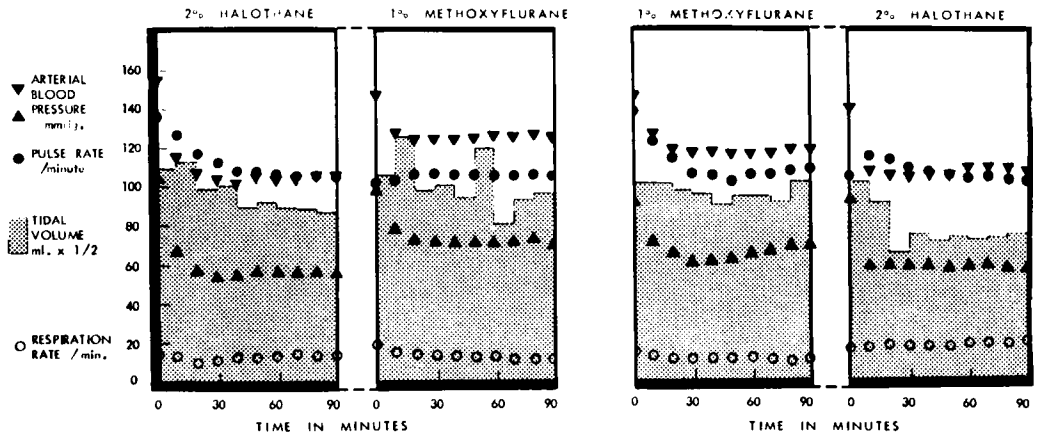

FIG. 1. Comparison of the cardiovascular and respiratory effects of halothane and methoxyflurane in dogs breathing spontaneously.

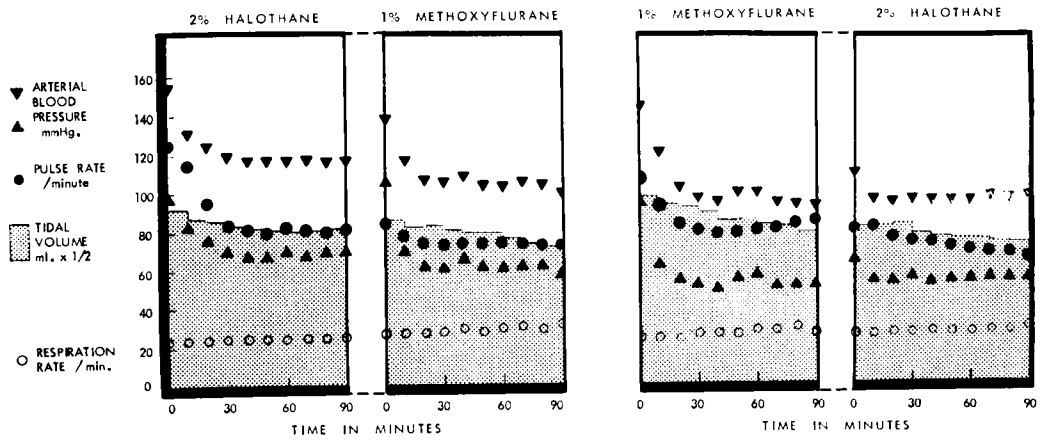

FIG. 2. Comparison of the cardiovascular and respiratory effects of halothane and methoxyflurane in dogs with augmented breathing.

The changes in respiration were not consistent among the 6 animals, but the trend showed a decrease in tidal volume during both agents. The tabulated data are not a true reflection of the respiratory response because the data on the tracings could only be analyzed for the periods when the animals were breathing, and not for the periods when apnea ensued (and it was necessary to augment breathing without anesthesia until spontaneous respiratory efforts on the part of the animal became evident). This depression of breathing to apnea occurred frequently with methoxyflurane and only occasionally with halothane, and it took much longer for recordable breathing to resume during anesthesia with methoxyflurane. This accounts for the apparent satisfactory tidal volume during the experiments as shown in figure 1.

When breathing was augmented with the Takaoka respirator, there was a slight increase in the rate of breathing and a slight decrease in tidal volume when either agent was used. These alterations resulted in the minor changes in the blood *p*H, P_{CO_2} and plasma bicarbonate (table 2).

Recovery from anesthesia was very slow at the end of these experiments, particularly when methoxyflurane was administered second. Even with the administration of oxygen for several hours after the experiments, the animals remained sluggish until the next day, and on occasions it appeared as if some of the animals would not survive. However, none of the 18 animals died during or after the study.

DISCUSSION

Since the early reports by Robbins, a large number of fluorinated hydrocarbon compounds have been studied as anesthetics. Each of these had some inherent property which precluded the desire for an extensive trial as a clinical anesthetic agent. Halothane finally emerged as the best of the many tested and has enjoyed ever increasing popularity during the past four years.[12, 13, 14] There remain three undesirable characteristics in the clinical use of halothane which are similar to that of chloroform and which require skill to manage or avoid; severe hypotension, respiratory depression and cardiac arrhythmias. One further clinical problem with halothane (which it shares with cyclopropane) is that even when adequate surgical analgesia is provided it does not usually cause adequate muscular relaxation, and in the provision of the desirable state there must be careful selection in order to avoid sharp cardiovascular depression. A characteristic of halothane anesthesia which has been described is the rapid recovery from the anesthetic state.[15, 16] This has been attributed to its weak analgesic effect and to its rapid elimination from the blood when a relatively light level of anesthesia has been maintained.[17, 18] Duncan and Raventós have shown that in mice and rats halothane is

rapidly absorbed during induction and its concentration in the arterial blood reaches an equilibrium with the inhaled concentration in a relatively short time after which it remains constant. On the other hand, the concentration of halothane increases slowly in the brain and liver, and increases rapidly in adipose tissue for many hours. Since the brain absorbs only a small amount of halothane and because the blood/gas partition coefficient of halothane is low, recovery from anesthesia is relatively rapid.[19] If these observations hold true in dogs and in man, it offers another explanation for the rapid 'recovery' from this anesthetic agent.

In extending the studies of fluorinated hydrocarbons and ethers, Van Poznak and Artusio found that methoxyflurane provides anesthetic conditions which were comparable to halothane, but with better muscle relaxation and with no significant incidence of cardiac arrhythmias.[20] Artusio and Wasmuth and their colleagues have studied methoxyflurane clinically and found that the laboratory observations were applicable to man.[1, 2] Unfortunately, both drugs share the potential of inducing hypotension and epinephrine-induced cardiac arrhythmias although the circulatory effects did not occur as precipitously with methoxyflurane as was seen with halothane, especially when they were administered with rigid control of the vapor concentration in the present study. An undesirable characteristic of methoxyflurane anesthesia is the prolonged postanesthetic period of recovery which occurs even after an apparently light level of anesthesia. Although the latter effect may reduce the requirement for postoperative analgesics, the prolonged hypnotic effect is a drawback which should be weighed heavily against its evident advantages.

The present report showed that when approximately equal hypnotic doses of methoxyflurane and halothane were administered to animals premedicated with perphenazine, neither agent caused cardiac arrhythmias nor evidence of myocardial depression when pulmonary ventilation was augmented. The occasional electrocardiographic changes that appeared during spontaneous breathing were indicative of tissue hypoxia when either agent was administered, although estimations of the oxygen saturation of the arterial blood did not reflect such an effect. Evidence of cardiac irritability that may be seen with halothane was probably prevented by premedicating the animals with perphenazine.[21] Hypotension and decrease in cardiac output were greater with halothane than with methoxyflurane. On the other hand, methoxyflurane had a more profound depressant effect on pulmonary ventilation which would require continuous attention to adequate breathing. There were no gross differences in the effect on electrolytes, blood sugar and cephalin cholesterol flocculation, that might reflect differences in metabolic changes or alterations in liver function.

In comparing the postanesthetic response of these animals with those similarly studied with halothane and halothane ether azeotrope,[10] it was evident that methoxyflurane was responsible for causing a prolonged and at times precarious recovery period.

On the basis of these observations, methoxyflurane may have slight advantages over halothane with respect to the circulation, but it has disadvantages with respect to respiration and post-anesthetic recovery. These various anesthetic properties make the selection of this new agent as difficult as deciding on the overall difference between chloroform and halothane.[22, 23, 24] Only extensive clinical trial may hold the final answer.

Summary and Conclusions

Crossover experiments were performed on 18 medium-sized mongrel dogs with 2 per cent halothane and 1 per cent methoxyflurane anesthesia. These concentrations were selected because they were the lightest that could be used to maintain a steady level of unconsciousness in the dog. Spontaneous breathing was allowed for 6 of the dogs unless apnea ensued. Breathing was augmented throughout the experiments with the other 12 dogs.

Cardiovascular and respiratory parameters were monitored continuously while halothane and methoxyflurane were each administered for 90 minutes on two occasions. Cardiac output estimations and tests of anion-cation balance, electrolytes, hematocrit, blood glucose and cephalin cholesterol flocculation were

done before each anesthetic and after the administration of each agent.

Two per cent halothane was less depressant to breathing than one per cent methoxyflurane, but was more depressant to the blood pressure and cardiac output. There were no essential differences in the metabolic effects by the two agents. Recovery from anesthesia appeared to be prolonged on account of the administration of methoxyflurane. It appeared as if a clinical choice between these two agents may be as difficult as that between chloroform and halothane.

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