ANESTHESIA LVII: A FURTHER STUDY OF THE ANESTHETIC PROPERTIES OF 1,1,1, TRIFLUORO-2,2-BROMOCHLORETHANE (FLUOTHANE)

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ROBBINS (1) studies the anesthetic properties of saturated and unsaturated fluorinated and mixed halogenated hydrocarbons and ethers of the lower members (up to four carbon atoms) of the aliphatic series. This study, extended by Lu, Ling, and Krantz (2), resulted in establishing the useful anesthetic properties of trifluoroethylvinyl ether (Fluoromar) (3). Raventós (4) reported on the anesthetic action of 1,1,1,trifluoro-2,2-bromochlorethane (Fluothane). A comprehensive study was subsequently conducted by him (5). Fluothane has had preliminary clinical trial in England by Bryce-Smith and O'Brien (6) and Johnstone (7).

The purpose of this investigation was to subject Fluothane * to a series of pharmacologic procedures employed in this laboratory for the study of other anesthetic agents.

METHODS AND RESULTS

Anesthetic Indexes.—The anesthetic index in mice was determined by the method previously described by Park, Truitt, and Krantz (8). Anesthetic indexes in the dog and monkey were determined by the procedure used by one of the authors (3). Ten dogs, 10 monkeys, and 125 mice were used in these studies.

The data, set forth in table 1, indicate that Fluothane is a potent anesthetic with a narrow margin of safety as measured by the anesthetic indexes in the three species of laboratory animals. For many of the ethers studied in this laboratory the spread between the volume in cubic centimeters per kilogram required to induce anesthesia and the volume necessary to produce respiratory arrest in dogs was 1 cc./kg. $\pm$ 0.15 cc. With Fluothane the corresponding value was 0.2 cc./kg. This is suggestive of our data for chloroform, namely, 0.17 cc./kg. for induction, and 0.27 cc./kg. for respiratory arrest (9). Our findings are not in accord with those of Raventós (5), who found the anesthetic index of Fluothane to be twice that of diethyl ether.

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* 1,1,1, Trifluoro-2,2-bromochlorethane was designated by Raventós as Fluothane, and this term is used throughout the paper, even though all of the material used was not supplied through the company by which Dr. Raventós is employed.

Blood Pressure Studies (Dog).—The effect of Fluothane on the blood pressure was determined in the following manner. Each of 5 dogs was lightly anesthetized with diethyl ether and blood pressure in the carotid artery was recorded. Respiratory tracings were made by means of a chest tambour. Administration of diethyl ether was discontinued, and each animal was allowed to recover to the stage of light anesthesia. Fluothane was administered, and surgical anesthesia (third plane) was produced in each animal and maintained for one-half hour. A typical tracing is shown in figure 1.

TABLE 1

ANESTHETIC INDEX: FLUOTHANE

	Fluothane (1,1,1, Trifluoro-2,2-Bromo-chlorethane)		Fluoromar (Trifluoroethyl-vinyl Ether)		Vinamar (Ethylvinyl Ether)		Diethyl Ether	
	AD_{50}	LD_{50}	AD_{50}	LD_{50}	AD_{50}	LD_{50}	AD_{50}	LD_{50}
Mice								
ED_{50}	1.53	3.10	4.65	12.70	5.60	16.50	6.08	16.20
f ED_{50}*	1.11	1.07	1.29	1.05	1.04	1.03	1.07	1.03
s†	1.19	1.12	1.29	1.11	1.10	1.05	1.15	1.06
fs*	1.07	1.06	1.09	1.04	1.03	1.02	1.03	1.04
Anesthetic Index (A.I.)	2.02‡		2.72		2.95		2.67	
f A.I.*	1.10		1.10		1.04		1.05	
Dog: dose (cc./kg.)								
Induction	0.28 ± 0.06		0.72 ± 0.13		0.56 ± 0.06		1.00 ± 0.23	
Arrest	0.55 ± 0.10		1.69 ± 0.29		1.66 ± 0.28		2.00 ± 0.31	
Anesthetic Index	1.90 ± 0.21		2.35 ± 0.27		3.00 ± 0.55		2.07 ± 0.43	
Monkey: (cc./kg.)								
Induction	0.19 ± 0.06		0.32 ± 0.07		0.37 ± 0.12			
Arrest	0.39 ± 0.15		0.98 ± 0.26		1.29 ± 0.47			
Anesthetic Index‡	2.10 ± 0.43		3.10 ± 0.45		3.50 ± 0.50			

* Error factor for $p = 0.05$.
† Slope of dose-response line.
‡ Anesthetic index significantly lower than that for Fluoromar, Vinamar and Diethyl Ether.

It is evident that surgical anesthesia with Fluothane elicits a marked depressor response in the drug. The depressor response evoked during Fluothane anesthesia appears to be a finding consistent with the observations of Raventós (5).

Electrocardiographic Studies (Dog).—Electrocardiographic studies were conducted on 5 dogs with a procedure similar to that employed in the blood pressure studies. Normal records were obtained followed

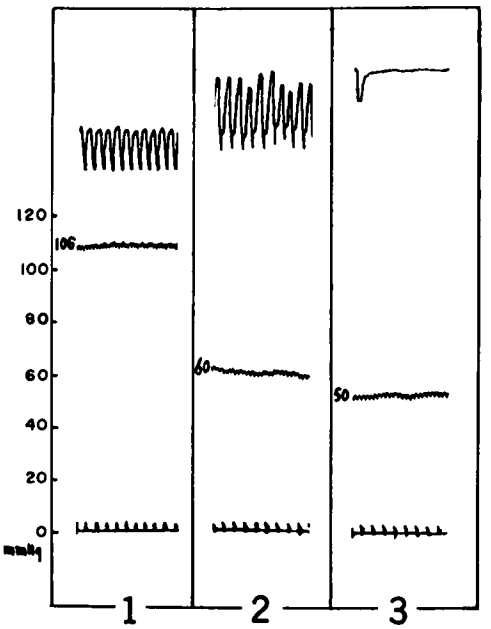

FIG. 1. Blood pressure of dog under Fluothane anesthesia. (1) Ethyl ether. (2) Fluothane. (3) Fluothane respiratory arrest. The top tracing is of respiration.

by records under surgical anesthesia with diethyl ether. The animal was permitted to recover partially, then anesthetized to the point of surgical anesthesia (third plane) with Fluothane. An electrocardiogram was taken, and after anesthesia was deepened to approaching respiratory arrest another electrocardiogram was taken. The electrocardiograms in the 5 dogs were relatively uniform. A typical record is shown in figure 2. Under surgical anesthesia with Fluothane the T wave was strongly inverted. Bradycardia occurred at the stage of threatened respiratory arrest.

Delayed Anesthetic Deaths.—Twenty white male rats were anesthetized with Fluothane for a period of thirty minutes. Each animal

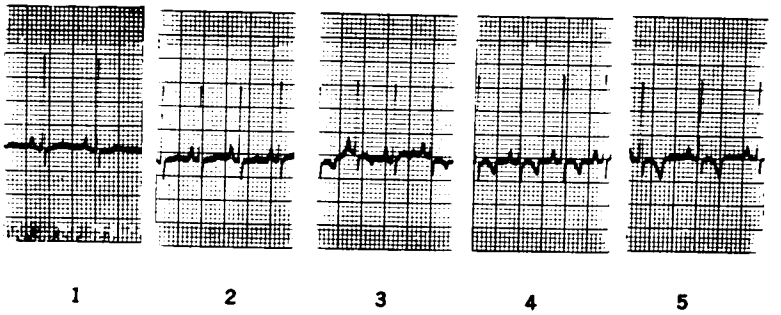

FIG. 2. Electrocardiogram of dog under ether and Fluothane. (1) Normal. (2) Ether surgical anesthesia. (3) Fluothane, light surgical anesthesia. (4) Fluothane, deep surgical anesthesia. (5) Fluothane, threatened respiratory arrest.

was placed in a large anesthetizing jar provided with soda lime and a liberal supply of oxygen. Anesthesia was induced with 0.25 cc. of Fluothane, and the animal was maintained at the surgical level of anesthesia by the addition of 0.05 cc. of the agent at necessary intervals. The animals were observed for a period of sixteen days. They remained in an excellent nutritional state, and there were no deaths.

Repeated Anesthesia (Rat).—Young male white rats weighing approximately 150 Gm. were divided into three groups of 4. Each rat was anesthetized for an hour by the procedure previously described. For the first group, anesthesia was conducted on three consecutive days, for the second group, on six days, and for the third group, on nine days. After the administration of anesthesia in each group was completed, the animals were killed for study of gross and histologic

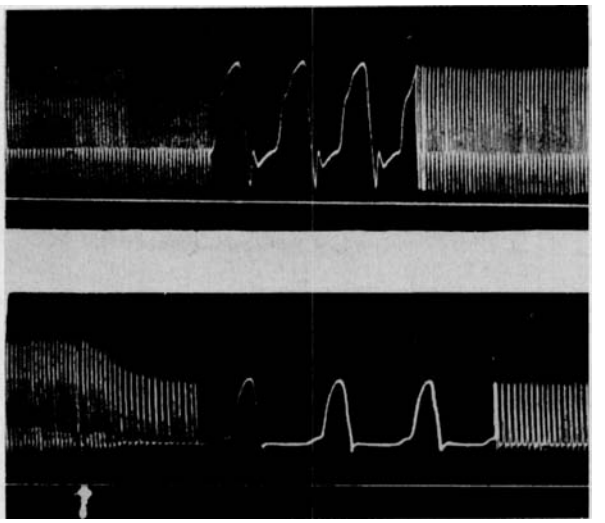

FIG. 3. Upper—normal tracing of frog's heart beat. Lower—same with 20 mg. per cent of Fluothane given at arrow.

changes in their livers, kidneys, and brains. There were no lesions in any of the organs of these animals attributable to anesthetic action.

Liver Function Tests (Dogs).—Four dogs were subjected to tests of liver function using Bromsulfalein as set forth in *New and Nonofficial Remedies.* Prior to, and one hour after, sixty minutes of anesthesia with Fluothane the test was conducted. After twenty-four hours the test was repeated. The percentage of dye excreted in all instances was not significantly different from that obtained prior to anesthesia.

Effect of Fluothane on the Perfused Heart (Frog).—Fluothane was dissolved in Howell-Ringer's solution and perfused through the hearts of 5 frogs. Solutions were prepared containing 20 mg. per cent, which is approximately the concentration Raventós (5) found in the dog's

blood under anesthesia. A typical tracing is shown in figure 3. It is evident that this concentration of Fluothane elicited a diminution in the amplitude of heart beat and a slowing of the heart rate of frogs.

Clotting Time and Hemolysis of Blood (Dog).—The clotting time of blood was determined in 4 normal dogs by the capillary tube method. The average value was one minute. In the same animals maintained under deep surgical anesthesia for sixty minutes the clotting time was again determined. There was no significant change in the clotting time of the blood in any of the dogs.

TABLE 2

OXYGEN CONSUMPTION IN MONKEY UNDER FLUOTHANE

Monkey Number	Body Weight (kg.)	Trial Number	Normal		Fluothane		Difference		
			Respirations per Minute	Oxygen Consumption (cc./kg. per hour)	Respirations per Minute	Oxygen Consumption (cc./kg. per hour)	Respirations per Minute	Oxygen Consumption (cc./kg. per hour)	Per Cent Decrease of Oxygen Consumption
1	2	1	52.0	2415	41.0	1575	−11.0	− 840	−32.73
		2	59.0	2415	55.7	1628	− 3.3	− 787	−32.61
		3	75.1	2363	51.1	1575	−23.9	− 788	−33.33
		4	66.7	3465	44.3	1785	−22.4	−1680	−48.50
2	3.3	1	68.5	1782	54.5	764	−14.0	−1018	−57.14
		2	68.0	1973	63.0	509	− 5.0	−1464	−74.19
		3	58.1	2100	51.3	1145	− 6.8	− 955	−45.45
		4	80.0	1909	45.0	1145	−35.0	− 764	−40.00
3	4.7	1	52.0	2011	59.8	938	+ 7.8	−1073	−53.33
		2	63.5	1497	59.5	804	− 4.0	− 693	−45.56
		3	66.0	1866	38.8	743	−27.2	−1123	−60.18
		4	77.0	1743	69.0	983	− 8.0	− 760	−43.60
Mean			65.5	2120	52.8	1128	−14.0	−1000	−47.18
Standard Deviation									±12.50
			Normal		Chloroform		Difference		
2	3.3	1	46.5	2164	33.3	1082	−13.2	−1082	−49.86
		2	72.3	1541	64.5	1206	− 7.8	− 335	−21.74
1	2	1	72.5	2520	62.1	1470	−10.4	−1050	−41.67
Mean			63.8	2075	56.6	1253	−10.5	− 822	−37.76

Volumes of 10 cc. of Fluothane, in varying concentrations in normal salt solution to which was added 0.1 cc. of defibrinated human blood, were maintained at 28 C. Twenty-five mg. per cent and 50 mg. per cent solutions of Fluothane produced no detectable hemolysis over a twenty-four-hour period of observation.

Respiratory Effects Under Deep Anesthesia (Monkey).—Control values for consumption of oxygen were determined on monkeys using a Benedict-Roth respirometer. The animal was anesthetized by the same procedure used for determining the anesthetic index until the amount of Fluothane administered was 50 per cent of that previously required for producing anesthetic arrest. The oxygen consumption

was again measured for a period of six minutes during which time anesthesia was maintained by the administration of 0.05 cc. of Fluothane per minute. The data are shown in table 2.

Effect on Oxygen Uptake of Heart.—Cardiac ventricular strips from the rat's heart were used. The Warburg technique was employed utilizing the specific details of Pearson, Hastings, and Bunting (10). Glucose was used as the substrate. Each strip of tissue was allowed to respire normally for forty minutes; Fluothane was then added and respiration was continued for another forty minutes. The data were calculated as percentage of oxygen uptake of the second period in terms of the oxygen uptake of the control period. In fifteen control experiments the percentage change in Q_{O_2} in the second period was 5.9 ± 2.5; in ten experiments with 20 mg. per cent of Fluothane, the percentage change during the second period was 24.6 ± 5.4. The diminution in cardiac oxygen uptake of 18.7 per cent (24.6–5.9) owing to the administration of Fluothane. This is significant, indicating that the myocardium under these conditions shares the respiratory depression produced by anesthesia with Fluothane in the intact animal.

Discussion

These studies have confirmed the findings of Raventós (5) in that Fluothane is a potent anesthetic agent in several species of laboratory animals. Our studies on dogs agree with the findings of other workers showing that anesthesia with Fluothane elicits a marked depressor response. In general, our electrocardiographic studies resembled those reported by Raventós (5). The anesthetic indexes determined in mice, dogs, and monkeys showed that Fluothane exhibited a low margin of safety. We did not find this agent to have an anesthetic index twice that of diethyl ether, as did Raventós (5), but found it to be only slightly safer than chloroform when measured under our experimental conditions and methods of calculation. In our experiments we frequently encountered difficulty in resuscitating animals which were brought to respiratory arrest with Fluothane. In several instances the animals (dogs and monkeys) could not be revived.

The depression of the oxygen uptake under Fluothane anesthesia in the monkey was marked. Table 2 indicates that oxygen utilization was depressed to a far greater degree under Fluothane anesthesia than those under ether or trifluoroethylvinyl ether (8). In this respect anesthesia under Fluothane resembles the chloroform anesthetic syndrome. The oxygen consumption of the rat's ventricular slices was depressed by anesthetic concentrations of Fluothane.

Summary

Fluothane was found in these experiments on animals to be a potent anesthetic agent with a low margin of safety. Its depressor re-

sponse and depression of oxygen consumption of the animal under anesthesia appear to be serious disadvantages in its use as an anesthetic agent.

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