OBSERVATIONS DURING EXPERIMENTAL AND CLINICAL USE OF FLUOTHANE

ROBERT W. VIRTUE, M.D., PH.D., KATHLEEN W. PAYNE, M.D.
LEONARD J. CARANNA, M.S., G. S. GORDON, M.D., R. R. REMBER, M.D.

WHEN a new anesthetic drug becomes available the question is immediately asked, "What is the degree of toxicity to the patient?" The statement has been made that halogenated derivatives of hydrocarbons have been notorious for deleterious effect upon certain tissues, particularly the liver (1). It has also been stated that in the saturated series, toxicity increases as the degree of halogenation increases (1). It has been noted that substitution of chlorine by fluorine in the chloroform molecule tends to diminish the toxicity of the agent (2). With the advent of Fluothane (1, 1, 1, trifluoro-2, 2-bromochlorethane) therefore the question, "What does this do to the liver?" would seem to be of paramount importance. Of the 8 atoms in the Fluothane molecule, 5 are halogens. Three of these, however, are fluorine atoms. Before one could feel safe in administering Fluothane to human subjects, it seemed necessary to learn whether or not this agent was toxic to the liver of animals. An answer to the following question was also sought with the use of dogs: "Does Fluothane sensitize the heart to injection of epinephrine as chloroform is known to do (3)?"

Later, measurements of variations in blood constituents were made during administration of Fluothane to surgical patients.

ANIMAL EXPERIMENTS

Procedure A.—To obtain a concept of the relative effects of ether and Fluothane on the liver, one dog was anesthetized with ether and oxygen for two hours. Another dog was anesthetized for two hours with Fluothane in 50 per cent each of nitrous oxide and oxygen. Endotracheal tubes were inserted in each case and the cuffs were inflated. The depth of anesthesia was maintained in a plane adequate for surgical anesthesia; that is, the lateral canthus reflex was obtunded. Control Bromsulphalein retention values were measured before anesthesia was induced and on succeeding days after exposure to anesthesia until the values had returned to normal. Thirty minute periods for dye excretion were used as they were deemed to be more rigorous than the frequently used forty-five minute periods (4). After Bromsulphalein values had returned to normal, crossover experiments were

Received from the Departments of Surgery, Medicine and Pathology, University of Colorado Medical School, Denver, Colorado, and accepted for publication April 2, 1958. Dr. Gordon is a Research Fellow, The National Heart Institute, U. S. Public Health Service, and Dr. Rember is a Trainee of the National Cancer Institute, Public Health Service.

done using the same animals. The one which originally received ether now received Fluothane and vice versa.

Procedure B.—After an interval of a week, procedure A was repeated using the same animals but reversing the order in which the agents were administered.

TABLE 1

BROMSULPHALEIN RETENTION IN DOGS AFTER ANESTHESIA WITH CHLOROFORM, ETHER AND FLUOTHANE

	Procedure	Anesthetic Agent	Per Cent BSP Retention at 30 minutes					
			Control	Days Postexposure				
				1	2	3	4	5
A	Two Hour Exposure							
	Dog 1	Ether	9	18	8			
		Fluothane	10	16	7			
	Dog 2	Fluothane	9	18	10			
		Ether	8	19	7			
B	Two Hour Exposure							
	Dog 1	Fluothane	11	17	4			
		Ether	9	15	7			
	Dog 2	Ether	9	24	9			
		Fluothane	7	17	5			
C	Four Hour Exposure							
	Dog 3	Fluothane	7	31	12	6		
		Ether	8	27	4			
	Dog 4	Ether	5	40	19	9		
		Fluothane	9	19	17	6		
D	Four Hour Exposure							
	Dog 2	Fluothane*	7	31	14	12	8	
		Ether	9	32	22	16	7	
	Dog 6	Ether	6	31	19	11	4	
		Fluothane*	7	34	24	14	10	
E	Dog 7	Chloroform	8	39	30	22	17	9
		Fluothane*	7	29	19	11	7	
		Ether	6	23	14	11	6	
	Dog 8	Fluothane*	7	30	21	14	10	
		Ether	8	28	19	16	9	
		Chloroform	11	49	29	19	14	8
	Dog 9	Ether	8	25	17	11	4	
		Chloroform	7	36	20	13	11	9
		Fluothane*	7	29	18	12	7	

* Dogs receiving Fluothane were fasted two days before anesthesia and had only 12 per cent alveolar oxygen. Dogs receiving ether and chloroform fasted only overnight and had 45 per cent alveolar oxygen.

Procedure C.—In order to increase the stress on the animals, procedure A was repeated with additional dogs except that the exposure time was prolonged to four hours of anesthesia in each case.

Procedure D.—To further increase the stress on the animals receiving Fluothane, procedure C was repeated with the additional conditions that the animals receiving Fluothane were fasted for two days before exposure and received only enough oxygen to maintain the alveolar oxygen partial pressure at 76 mm. of mercury. (Atmospheric pressure in Denver is 630 mm. of mercury.) One of the animals used was dog 2 which had been used previously in procedure A.

Procedure E.—To obtain comparable information on the exposure of animals to ether, Fluothane and chloroform, and to rule out unknown possibilities which conceivably could affect results, a Latin-square design experiment was utilized in which each of three dogs was exposed to each of the three anesthetic agents in order of succession as follows:

	First	Second	Third Exposure
Dog 7	Chloroform	Fluothane	Ether
Dog 8	Fluothane	Ether	Chloroform
Dog 9	Ether	Chloroform	Fluothane

Nearly the same conditions were employed as in procedure D; namely, control Bromsulphalein determinations before anesthesia and repeated determinations daily postanesthesia were made until the values had returned to normal. Several days were allowed to elapse before exposure to the next anesthetic agent. A two day fast was allowed before exposure of the animals to the anesthetic agent and the animals receiving Fluothane were maintained with an alveolar partial pressure of approximately 285 mm. of mercury. They received ether and oxygen or chloroform and oxygen through an open T-tube connected to a cuffed endotracheal tube. Each period of anesthetic exposure was four hours. Venous *p*H and alveolar oxygen values were determined at frequent intervals and at the termination of each exposure.

Procedure F.—Four dogs were given intravenous injections of epinephrine according to the technique of Meek, Hathaway and Orth (3). Electrocardiographic tracings were obtained. The animals were then anesthetized with Fluothane and identical doses of epinephrine again injected.

Procedure G.—Autopsies were performed after sacrificing the dogs with overdoses of nembutal, Fluothane, or chloroform.

Results with Animals

Procedures A, B, C, and D of table 1 indicates that Bromsulphalein retention following ether anesthesia was almost identical to that following Fluothane anesthesia. The order of administration of these drugs produced no effect.

Procedure E of table 1 presents data from the Latin-square experiment. The use of ether and Fluothane was obviously followed by strikingly similar results. The data were placed in a three way one-per-cell analysis-of-variance design. It is clear from table 2 that dogs-by-agents interaction term was significant, each at the 5 per cent level. Calculations using Satterthwaite's approximation (5) showed that results with chloroform were significantly different from those using either Fluothane or ether, with a 0.03 level of confidence. The order of administration and the individual dog did not affect the results.

*p*H values of blood taken during and at the end of these anesthetic exposures ranged from 7.3 to 7.45.

In procedure F, of the 4 dogs receiving epinephrine while anesthetized with Fluothane, 2 went into ventricular fibrillation and a third showed ventricular tachycardia.

In procedure G, at autopsy, no outstanding organic changes were found. The liver of animal 7, killed with Fluothane, showed slight

TABLE 2

STATISTICAL ANALYSIS OF LATIN-SQUARE EXPERIMENTS USING DOGS RECEIVING FLUOTHANE, ETHER AND CHLOROFORM

	Sum of Squares	*d.f.*	Mean Square	*F*	*p*
Dogs	126.389	2	63.195	3.17 n.s.	
Agents	624.889	2	312.445	6.71*	.03
Days	2,566.528	3	855.509		
Dogs × Agents	79.777	4	19.944	3.96	.05
Dogs × Days	17.389	6	2.898		
Agents × Days	98.889	6	16.482	3.27	.05
Agents × Dogs × Days	60.445	12	5.037		
Total	3,574.306	35			

* 12 *d.f.*

vacuolization which was predominantly periportal (not central). This vacuolization is common in dogs obtained from the pound who have undergone no experimental procedure. There was no evidence of fatty alteration. No central necrosis was found in any of the animals.

OBSERVATIONS AND METHODS WITH SURGICAL PATIENTS

When evidence had been obtained that Fluothane did not affect the livers of dogs as did chloroform, when a report (6) appeared concerning anesthetization of 500 persons with Fluothane, and when a reliable instrument for accurately delivering small concentrations of Fluothane became available, measurements were made with surgical patients receiving Fluothane for production of anesthesia. These patients were chosen on the basis of their being scheduled for surgery at least two days preoperatively so that control determinations of Bromsulphalein

TABLE 3

OPERATIONS PERFORMED USING FLUOTHANE ANESTHESIA

Patient	Sex	Age (Years)	Weight (pounds)	Surgical Procedures	Anesthesia Time (minutes)
1	F	52	105	Moore prosthesis	300
2	F	53	150	Excision ovarian tumor	200
3	F	30	119	Thyroidectomy	245
4	F	38	142	Cholecystectomy, colostomy	265
5	M	66	166	Prostatectomy	210
6	M	55	133	Gastrectomy	335
7	F	39	145	Vaginal hysterectomy	205
8	M	77	115	Hemicolectomy, colostomy	330
9	F	68	125	Vaginal hysterectomy	200
10	M	57	126	Excision bladder tumor	150
11	M	79	140	Polypectomies, colostomies	380
12	M	63	148	Prostatectomy	230

retention (4), blood volume (7, 8), bleeding time (9) and clotting time (10) could be made. Blood glucose (11) and blood urea (12) values as well as some urea clearance (13) determinations were done. The type of surgical procedures performed will be seen in table 3.

Twelve patients were anesthetized with a flow of 500 cc. of nitrous oxide and 500 cc. of oxygen using a semiclosed circle system, with addition of known amounts of Fluothane using concentrations of about 2 per cent for induction. This proportion of nitrous oxide and oxygen had been found (14) to afford adequate oxygenation. The flow of Fluothane was diminished as anesthesia progressed. Endotracheal intubation was performed using no relaxing agents other than Fluothane. After one hour of anesthesia without surgery, observations

TABLE 4

PHYSIOLOGICAL VARIATIONS USING FLUOTHANE IN TWELVE PATIENTS

	Preoperative Day		Preanesthesia		One Hour Fluothane		First Postoperative Day		Other
	Average	Standard Error of Mean	Average	Standard Error of Mean	Average	Standard Error of Mean	Average	Standard Error of Mean	
Blood glucose (mg. per cent)	94	2.05	94 *A*	3.15	128 *B*	5.81	94 *C*	5.27*	
Blood urea (mg. per cent)	22	3.37	21	3.46	20	3.18	20	2.57	
Hematocrit (per cent)	45	1.44			43	0.88			
Total blood volume (cc.)	4,691	263			4,765	237			
Bleeding time (seconds)	151	15.8			149	11.6	140	13.1	
Coagulation time (seconds)	519	26.3			456	24.0	465	31.1	
Bromsulphalein retention (per cent in 30 minutes)	8	0.98			10	2.80	13	2.40	8 (Fourth day in 5 patients. Earlier in the other 7)
Urea clearance (ml. per minute)	68	10					72	11†	

* 6 patients not receiving intravenous glucose
† 6 patients
Critical ratio A − B = 5.13
B − C = 4.31

TABLE 5

SERIAL SERUM TRANSAMINASE (SIGMA-FRANKEL UNITS) VALUES FOLLOWING FLUOTHANE ANESTHESIA

Patient	Pre-Op. Control		8-12 Hr.		24 Hrs. Day 1		Day 2		Day 3		Day 4		Day 5		Day 6		Day 7		Day 8		Day 9	
	SGOT	SGPT	SGOT	SGPT	SGOT	SGPT	SGOT	SGPT	SGOT	SGPT	SGOT	SGPT	SGOT	SGPT	SGOT	SGPT	SGOT	SGPT	SGOT	SGPT	SGOT	SGPT
1	18	8	16	5	14	5	16	7			14	2	15	7	16	10			17	15	18	14
2	11	8	13	5	18	10	15	6	17	7			16	10								
3	11	14	12	10	13	8	11	14	24	19	20	16	26	20			13	10			25	15
4	11	4	12	1	18	9	18	5	17	8			24	12								
5	15	3	21	9	9	8	11	6	13	3			22	10			18	11				
6	16	14	11	10	11	4	15	10														
7	14	7	9	5	12	8	16	8	13	5		6										
8	15	7	14	3	13	3	14	6	18	4	20	5	14	8			16	4			16	7
9	10	8	14	5	17	6	20	8	10	13	16	13	51	23			27	19				
10	13	6	11	7	15	12	10	8	21	9												

Patient	Operations
1	Abdominal exploration, excision left renal cyst
2	Transurethral resection
3	Abdominal hysterectomy, right salpingo-oophorectomy
4	Dilatation and curettage, conization, excision Bartholin cyst
5	Dilatation and curettage, cervical conization
6	Dilatation and curettage, cervical conization
7	Bilateral tubal ligation
8	Split thickness skin graft to left leg from bilateral thighs
9	Wedge resection right ovary, hysterectomy, bilateral salpingectomy, left oophorectomy
10	Dilatation and curettage, cervical conization

were again made to determine the effect of the agent alone on the subject. Bromsulphalein, blood urea, blood glucose, bleeding and clotting times were measured. The next day, the values were again determined and Bromsulphalein retention was followed until values returned to normal.

Blood samples for thymol turbidity tests (15) and serum transaminase values (16) were obtained from 10 other patients. Control samples were drawn the day prior to surgery. Samples of thymol turbidity tests were again drawn the fifth postoperative day on 6 patients. Samples for transaminase determinations were obtained from 10 patients at eight to twelve hours following surgery, and at daily intervals for three to nine days after surgery.

TABLE 6

THYMOL TURBIDITY VALUES BEFORE AND AFTER FLUOTHANE ANESTHESIA IN 5 PATIENTS

Patient	Preoperative Value	5-Day Postoperative Value
1	3.0	2.0
2	4.5	4.0
3	2.5	3.0
4	1.5	2.0
5	3.0	2.0

RESULTS WITH PATIENTS

Table 4 indicates that blood glucose was significantly increased during an hour of Fluothane anesthesia and that it had returned to normal by the next morning in those patients who were not receiving infusions containing glucose. Urea, blood volume, bleeding and clotting time and urea clearance were essentially unchanged. BSP retention was moderately elevated and returned to normal within a reasonable time. The effect of surgery on the time for return to normal could not be ascertained.

Table 5 presents data on serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT) values. A rise of SGOT values in patient 9 is unexplained, but this did not occur until the fifth day postoperatively. The other values all fall well within the expected range for surgery using other anesthetic agents. Thymol turbidity figures showed no abnormal values on the fifth day postoperatively (table 6).

DISCUSSION

Conditions were deliberately chosen for the animal experiments which would tend to accentuate any ill effect that Fluothane might have on the liver. It has been shown (17, 18) that fasting and a low concentration of oxygen each produce deleterious effects on the liver of dogs receiving chloroform anesthesia, consequently a combination of

these conditions was used for these experiments. Since the results were equivalent to those obtained from dogs with ether anesthesia, one sees evidence that Fluothane does not easily injure the liver. Chloroform produced significantly greater retention of BSP than did either ether or Fluothane.

The immediate severe reactions to epinephrine in dogs anesthetized with Fluothane made it unnecessary to use many animals for this procedure. The drug showed a definite sensitization of the myocardium of the dog to epinephrine.

While Bromsulphalein retention does not measure all phases of liver activity, the results obtained both with dogs and patients signify that this function was no more severely disturbed by Fluothane than by ether anesthesia. Although the blood glucose of patients rose consistently during Fluothane anesthesia, it did not rise to as great an extent as would be expected using ether anesthesia (1). Kidney function of patients as measured by urea clearance tests and other possible metabolic changes as measured by blood urea, bleeding and clotting times and blood volumes were seemingly minimal. Thymol turbidity tests showed no deleterious effects of Fluothane on the liver.

The range of glutamic oxaloacetic serum transaminase values in a few other conditions involving the liver has been published (19, 20, 21). Generally accepted normal values (Sigma-Frankel units) are as follows: SGOT, 8 to 40, and SGPT 5 to 35. Values of borderline significance 40 to 50 (SGOT), and 35 to 45 (SGPT). Table 4 would indicate that anesthesia with Fluothane lasting 41 to 174 minutes did not result in any overt hepatic necrosis as judged by the serum transaminase tests. Table 5 presents data on the thymol turbidity tests which revealed no hepatoxic effect of Fluothane.

Clinically our observations on Fluothane have been in general accord with those of others who have had larger series of patients (6, 22). We observed an easy induction with 2 per cent Fluothane; we observed that respiration could be controlled quite easily with a few manipulations of the breathing bag; we observed that hypotension was easily produced with a mild overdose of the drug; we observed that relaxation adequate for orotracheal intubation could be produced; we observed that diminution of laryngeal and pharyngeal reflexes occurred easily, and we observed a rapid recovery from the effects of the anesthetic with minimal postoperative vomiting. As mentioned by others, Fluothane is an extremely potent agent. It is not safe to use unless an apparatus for producing controlled low concentrations is at hand. Our standard machines (Heidbrink, Foregger) could not be calibrated to deliver safe and consistent concentrations of Fluothane.

Summary

Crossover experiments in 6 dogs stressed by moderate hypoxia and a two day fast indicated that Bromsulphalein retention after four

hours of Fluothane anesthesia was no greater than that following ether anesthesia in the same dogs unstressed by fasting or hypoxia.

Observations with 3 dogs in experiments of Latin-square design indicated that Bromsulphalein retention was significantly greater in dogs given chloroform than in dogs given ether under the same conditions or in dogs given Fluothane under mildly hypoxic conditions.

Two of 4 dogs given intravenous epinephrine during Fluothane anesthesia had ventricular fibrillation; a third showed ventricular tachycardia.

Twelve patients given Fluothane with 500 cc. per minute each of nitrous oxide and oxygen for an hour before surgery showed a consistent rise of blood glucose. Blood urea, blood volume, bleeding and clotting times remained at control levels. Urea clearance function did not seem to be affected. BSP retention increased moderately and returned to control levels within a few days.

Thymol turbidity tests on five other patients showed no abnormality on the fifth post-Fluothane day. Serum transaminase values at eight to twelve hours postanesthesia and on several succeeding days were normal in 10 other patients who had Fluothane anesthesia which lasted from 41 to 174 minutes.

The authors wish to acknowledge the assistance in the statistical evaluations by Dr. William Sawrey and the technical assistance of Miss Dorothy Marco. This study was aided by grants from the Imperial Chemical Industries, Ltd., Manchester, England, and from the Continuing Research Fund of the University of Colorado Medical Faculty.

REFERENCES

1. Adriani, J.: The Chemistry of Anesthesia, Springfield, Illinois, Charles C Thomas, Publishers, 1946.
2. Suckling, C. W.: Some Chemical and Physical Factors in Development of Fluothane, Brit. J. Anaesth. 29: 466 (Oct.) 1957.
3. Meek, W. J., Hathaway, H. R., and Orth, O. S.: Effects of Ether, Chloroform and Cyclopropane on Cardiac Automaticity, J. Pharmacol. & Exper. Therap. 61: 240 (Nov.) 1937.
4. Rosenthal, S. M., and White, E. C.: Clinical Application of Bromsulphalein Test for Hepatic Function, J. A. M. A. 84: 1112 (April 11) 1925.
5. Anderson, R. L., and Bancroft, T. A.: Statistical Theory in Research, New York, New York, McGraw-Hill Company, 1952, pp. 350.
6. Johnstone, M.: Human Cardiovascular Response to Fluothane Anaesthesia, Brit. J. Anaesth. 28: 392 (Sept.) 1956.
7. Crispell, K. R., Porter, B., and Nieset, R. T.: Studies of Plasma Volume Using Human Serum Albumin Tagged with Radioactive Iodine, J. Clin. Investigation 29: 513 (May) 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. & Obst. 91: 458 (Oct.) 1950.
9. Duke, W. W.: Relation of Blood Platelets to Hemorrhagic Disease, J. A. M. A. 55: 1185 (Oct. 1) 1910.
10. Lee, R. I., and White, P. D.: Clinical Study of Coagulation Time of Blood, Am. J. Med. Sci. 145: 495 (1913).
11. Nelson, N.: Photometric Adaption of Somogyi Method for Determination of Glucose, J. Biol. Chem. 153: 375 (May) 1944.
12. Karr, W. G.: Method for Determination of Blood Urea Nitrogen, J. Lab. & Clin. Med. 9: 329 (Feb.) 1924.

13. a. Folin, O., and Youngberg, G. E.: Note on Determination of Urea in Urine by Direct Nesslerization, J. Biol. Chem. 38: 111 (May) 1919.
13. b. Youngberg, G. E.: Removal of Ammonia From Urine Preparatory to Determination of Urea, J. Biol. Chem. 45: 391 (Feb.) 1921.
14. Weaver, R. H., and Virtue, R. W.: Blood Oxygenation as Affected by Tidal Volume and Tension of Nitrous Oxide-Oxygen Inhaled at One Mile Altitude, ANESTHESIOLOGY, 16: 57 (Jan.) 1955.
15. Hepler, O. E.: Manual of Clinical Laboratory Methods, Springfield, Illinois, C. C Thomas Publishing Company, 4th Ed., 1949, pp. 122.
16. Reitman, S., and Frankel, S.: Colorimetric Method for Determination of Serum Transaminase Activity, Sigma Chemical Company Technical Bulletin, Number 505 (Aug. 10) 1957.
17. Goldschmidt, S., Vars, H. M., and Ravdin, I.: Influence of Foodstuffs Upon Susceptibility of Liver to Injury by Chloroform, and Probable Mechanism of Their Action, J. Clin. Investigation 18: 277 (May) 1939.
18. Goldschmidt, S., Ravdin, I. S., and Lucke, B.: Anesthesia and Liver Damage. I. Protective Action of Oxygen Against Necrotizing Effect of Certain Anesthetics on Liver, J. Pharmacol. & Exper. Therap. 59: 1 (Jan.) 1937.
19. Chinsky, M., Shmagranoff, G. L., and Sherry, S.: Serum Transaminase Activity, Observations in Large Group of Paients, J. Lab. & Clin. Med. 47: 108 (Jan.) 1956.
20. Molander, D. W., Sheppard, E., and Payne, M. A.: Serum Transaminase in Liver Disease, J. A. M. A. 163: 1461 (April 20) 1957.
21. Shay, H., and Siplet, H.: Study of Chlorpromazine Jaundice, Its Mechanism and Prevention, Gastroenterology 32: 571 (April) 1957.
22. Stephen, C. R., Grosskreutz, D. C., Lawrence, J. H. A., Fabian, L. W., Bourgeois-Gavardin, M., and Coughlin, J.: Evaluation of Fluothane for Clinical Anaesthesia, Can. Anaes. Soc. J. 4: 246 (July) 1957.