Clinical Experiences with Fluothane *

A New Nonexplosive Anesthetic

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SURGEONS as well as anesthesiologists have long been interested in obtaining a potent nonexplosive nonflammable inhalation anesthetic. Recently, Fluothane ** (2-bromo-2 chloro-1-1-1-trifluoroethane) has been investigated as a potential solution to this problem. Its physical properties are more fully described by Raventos [6] but in essence it is a volatile liquid which, in addition to being nonexplosive and nonflammable, is pleasant smelling, does not react with soda lime, and is stable in dark bottles. It is the purpose of this paper to describe clinical experiences with this agent as the principal anesthestic agent for 500 surgical procedures.

Clinical Material and Methods of Administration

The types of operation performed, the age distribution of the patients, and the duration of anesthesia are listed in Tables 1, 2, and 3. Half of these cases were major and half minor procedures. Fifty-eight per cent of the patients were females. Of these patients 48 per cent were considered good anesthetic risks, 36 per cent fair risks, and 16 per cent poor risks. In all but a few of the last cases in this series anesthesia was given using standard Heidbrink and McKesson machines and placing the Fluothane in the ether vaporizer. These later cases were done using the "Fluotec" vaporizer, a temperature compensated device that delivers a known concentration of vapor over a wide range of flows. The value of being able to deliver a known concentration of vapor will be discussed later.

It soon became apparent that due to the extreme potency of Fluothane, very minor changes of the setting of the ether vaporizer of these machines resulted in a great change in the level of anesthesia. For this reason we removed the wick from the vaporizer and in this fashion were better able to control the concentration of vapor delivered to the patient. Although the actual percentage of vapor delivered at a given dial setting was not known, since this would vary with flow rate and temperature, dangerously high concentrations of vapor could be avoided much more easily when the wick was not used.

That Fluothane can be given with a wide variety of other agents and can be administered in many ways is shown by Tables 4 and 5. As peripheral vascular collapse has been reported by Johnstone [4] when Fluothane is given with d-tubocurare, the muscle relaxant used in all these cases was succinylcholine. In the great majority of instances where barbiturate was used, only the amount necessary for induction of anesthesia, usually from 100 mg. to 250 mg. of thiopental sodium, was administered. Because of its potency, when used with the closed circle absorber technic it was soon

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** The Fluothane used was supplied by Ayerst Laboratories.

discovered that dangerously high concentrations of Fluothane vapor could rapidly and insidiously be built up with resultant sudden depression of respiration and circulation. For this reason we have abandoned its use in the closed system and now administer it using semi-closed or non-rebreathing technic. In this way dangerous concentrations of vapor can be avoided more easily.

These anesthetics were given by personnel having a wide range of experience and training (Table 6). However, those individuals with relatively little training were always closely supervised by some one with considerably more training and experience. This was done in an effort to evaluate the relative safety of this agent in hospitals where it might be used by those not completely familiar with and trained in technics of general anesthesia.

TABLE 1. *Type of Surgery*

	No. Cases	Per Cent Total
Upper abdominal	43	8.6
Lower abdominal	44	8.8
Intrathoracic	23	4.6
Body wall	70	14.0
Back and extremities	70	14.0
EENT	30	6.0
Other head and neck	39	7.8
Rectal, vaginal, perineal	110	22.0
Cysto. and T.U.R.	53	10.6
X-ray diagnostic procedures	18	3.6
	500	100.0

TABLE 2. *Age Distribution, Six Weeks to 87 Years*

	Cases	Per Cent
Less than 1	12	2.4
1–4	28	5.6
5–14	51	10.2
15–29	77	15.4
30–44	122	24.4
45–59	125	25.0
60–74	73	14.6
Over 75	12	2.4
	500	100.0

TABLE 3. *Duration of Anesthesia*

Shortest 5 min. Longest 7 hours 15 min.	No. Cases	Per Cent
Less than 30 min.	109	21.8
30–59 min.	119	23.8
60–119 min.	144	28.8
120–179 min.	61	12.2
Greater than 180 min.	67	13.4
	500	100.0

TABLE 4. *Anesthetic Combinations Used*

	No. Cases	Per Cent
Fluothane-O_2	66	13.2
Fluothane-O_2-barbiturate	16	3.2
Fluothane-O_2-relaxant	4	0.8
Fluothane-O_2-barbiturate-relaxant	3	0.6
Fluothane-O_2-N_2O	94	18.8
Fluothane-O_2-N_2O-barbiturate	165	33.0
Fluothane-O_2-N_2O-relaxant	8	1.6
Fluothane-O_2-N_2O-barbiturate-relaxant	97	19.4
Fluothane with other combinations	47	9.4
	500	100.0

Clinical Observations

Induction: The usual preoperative medication for these patients was 50 mg. to 100 mg. of meperidine, or a comparable dose of morphine, and either atropine or scopolamine given one half to one hour preceding induction of anesthesia. Most patients were relaxed but not noticeably sedated prior to induction. In the overwhelming majority when Fluothane was used alone or in conjunction with thiopental sodium or nitrous oxide, induction was smooth and rapid and free from coughing, secretions, and excitement. This agent has a sweetish odor which is not unpleasant and only very rarely did the patients find induction an unpleasant experience when questioned following operation.

Maintenance: Maintenance of a constant plane of anesthesia requires considerable attention and care as the potency of Fluo-

thane is such that changes in depth of anesthesia can occur with great rapidity. The physical signs of the stages of anesthesia as described by Guedel are hard to apply to Fluothane. Not infrequently the patient while apparently adequately "hypnotic" was not adequately "analgesic" as shown by movement and changes in respiration and blood pressure at the time of skin incision. In this regard, we have found the single most important sign of the level of anesthesia to be the blood pressure.

Cardiovascular System: In our hands one of the main drawbacks of Fluothane proved to be hypotension during induction. The degree and incidence of blood pressure fall during induction comparing 500 cases of Fluothane anesthesia with 500 cases of general anesthesia chosen at random over the same time interval and administered by the same personnel is shown (Table 7). For this purpose we have arbitrarily defined induction as the first 30 minutes of anesthesia. As this shows hypotension was not universal as almost 16 per cent of patients had a rise of pressure during this time, but marked degrees of hypotension were much more common in the patients receiving Fluothane. This is similar to the findings of induction hypotension reported by Stephen *et al.*[8] The degree of hypotension appeared to be closely related to the depth of anesthesia and was readily reversible by lightening the anesthesia or by giving a pressor drug. A comparison of the first 250 cases with the second 250 cases showed no decrease in the incidence of hypotension as we became more familiar with the use of the agent. Two cases in this series were cancelled when the pressure had fallen to unobtainable levels during induction. In all other cases the skin remained warm, pink, and dry and the patients had dilated veins and full pulses. This was true even when the systolic pressure was only 50 or 60 mm. of mercury.

Bradycardia as well as hypotension was a frequent accompaniment of the deeper planes of anesthesia. This could rapidly be abolished by giving atropine intravenously. This would not only increase the heart rate to more normal levels but also was sometimes effective in raising the blood pressure. The importance of atropine as the anticholinergic drug of choice for premed-

TABLE 5. *Method of Administration*

	No. Cases	Per Cent
Open drop	7	1.4
Closed circle	83	16.6
Semi-closed circle	350	70.0
Non-rebreathing	60	12.0
	500	100.0

TABLE 6. *Anesthesia Administered by:*

	No. Cases	Per Cent
Staff anesthesiologist	188	37.6
Resident anesthesiologist	94	18.8
Staff nurse anesthetist	97	19.4
Student nurse anesthetist (Supervised by Staff Nurse or anesthesiologist)	40	8.0
Intern (Supervised by anesthesiologist)	62	12.4
Medical student (Supervised by anesthesiologist)	19	3.8
	500	100.0

TABLE 7. *Blood Pressure Changes During Induction*

	Fluothane		Other General Anesthetics	
	Cases	Per Cent	Cases	Per Cent
Pressure increase	79	15.8	164	32.8
Less than 20 mm. Hg fall	179	35.8	218	43.6
20–40 mm. Hg fall	139	27.8	67	13.4
40–60 mm. Hg fall	38	7.6	12	2.4
Greater than 60 mm. Hg fall	17	3.4	3	0.6
Pressures not recorded	48	9.6	36	7.2
	500	100.0	500	100.0

ication when Fluothane anesthesia is anticipated has been stressed by Johnstone.[4]

Cardiac arrhythmias appeared to us clinically to be no more frequent than with the other general anesthetic agents commonly used.

There were two cardiac arrests in this series and no fatalities. One of these was in a child undergoing tonsillectomy. In this case it is felt the cardiac arrest was probably due to an overdose of Fluothane. The other cardiac arrest occurred during a pneumonectomy. In this case arrest followed hypoxia due to a mechanical blocking of the endotracheal tube and is felt was not related to the anesthetic agents.

Respiration: Fluothane is a potent respiratory depressant particularly in deeper planes of anesthesia. This depression is accompanied by a tachypnea so that even though minute volume may be maintained for a time, effective alveolar ventilation suffers more rapidly and as a result hypoxia and hypercarbia may occur. It is, therefore, frequently necessary for respiration to be assisted or controlled if the patient is to be effectively ventilated. At the same time, the anesthetist must exercise great care when assisting or controlling respirations to avoid "pumping the patient down" with this very potent agent as he may very easily and rapidly have the patient in a much deeper plane of anesthesia than is desirable or necessary for the surgical procedure. Control of respiration is very easy with Fluothane even in light planes of anesthesia. Relatively high concentrations of vapor are readily tolerated by the patient without coughing, laryngospasm, or secretions due to its lack of irritating effects.

We have been impressed clinically with the ease with which Fluothane is tolerated by the asthmatic. Whether this is due to a dilating effect on the smooth muscle of the tracheo-bronchial tree is unknown, but anesthesia in these patients has been characterized by ease of inflation and an absence of secretions and wheezing respirations.

Muscle Relaxation: Good muscle relaxation even for upper abdominal operations can be obtained with Fluothane alone. However, as the degree of relaxation appears to vary with the depth of anesthesia, sufficient depth necessary for production of relaxation, especially in upper abdominal surgery, usually is accompanied by a pronounced fall in blood pressure as well as respiratory depression. Since we do not feel it is wise to subject patients to this hypotension unnecessarily, we generally use a muscle relaxant so that anesthesia can be maintained in a lighter plane and thereby reduce the chance of a blood pressure fall. Endotracheal intubation under Fluothane is not difficult and can usually be accomplished within a few minutes of induction of anesthesia. The endotracheal tubes appear to be well tolerated and there is not much associated bucking or coughing.

Effect on Liver Function: As halogenated compounds are prone to cause liver damage, liver function tests were performed on 14 patients preoperatively and on the first, third, and fifth postoperative days for evidence of liver damage following Fluothane anesthesia. All of these patients received only Fluothane and oxygen for anesthesia and none had evidence or history of liver disease, carcinoma, or infection. Upper abdominal operations were excluded as it was feared that unrecognized surgical trauma to the liver might occur during these cases. The average age of the patients was 39.9 years and the average duration of anesthesia was one hour and 54 minutes. Blood was given to only one patient. Only one had known hypotension or hypoxia. This patient was used as a subject for respiratory studies and the anesthesia was purposely carried to greater depths than was necessary for the surgical procedure. As a result he had marked respiratory and circulatory depression that could not but result in periods of hypoxia during part of his anesthesia. This patient had an elevated B.S.P. retention and serum

bilirubin on his first postoperative day, and an elevated serum alkaline phosphatase on the first and fifth days. Three other patients had elevated B.S.P. retention postoperatively. One was on the first and two on the third postoperative days. Two others had decrease in retention over slightly elevated preoperative levels. In the other liver function studies one or two patients had slightly elevated values postoperatively while a similar number had decreased values over slightly elevated preoperative figures. The average values of this study are given (Table 8). This compares favorably with a series of similar patients receiving anesthesia with commonly used agents reported by Fairlie *et al.*[3] Similar findings regarding possible hepatotoxicity have been reported by Stephen [8] and Little.[5]

Recovery: We have been impressed with the lack of secretions in patients receiving Fluothane and have felt that these patients usually awaken more rapidly than comparable cases anesthetized by conventional agents. Table 9 shows the decreased incidence of nausea and vomiting comparing 450 cases of Fluothane anesthesia with a similar number of cases using other general anesthetics chosen at random and given by the same personnel. The period of observations for this study was limited to the patients' stay in the postoperative recovery room where it was felt they would be more closely watched than on their return to the floors, and the observations could be made by the same personnel. Antiemetic drugs were not given to these patients preoperatively or while in the recovery room.

TABLE 8. *Effect of Fluothane on Liver Function—14 Cases*

	Preop.	Postop. Days 1	3	5
B.S.P. retention (%)	2.64	2.0	1.7	0.0
Total serum bilirubin (mgm.%)	0.56	0.54	0.42	0.33
Alkaline phosphatase (Bodansky Units)	2.96	2.24	2.37	2.98
Thymol turbidity (Turbidity Units)	2.89	2.49	2.41	1.96
Cephalin cholesterol flocculation (Units)	0.93	1.21	1.14	0.62

TABLE 9. *Nausea and Vomiting in Recovery Room*

	Nausea Alone	Nausea and Vomiting
Fluothane (450 cases)	14 patients 3.1 per cent	46 patients 10.2 per cent
Other general anesthetics (450 cases)	27 patients 6.0 per cent	77 patients 17.1 per cent

Discussion

The main advantages of Fluothane are: 1) potency, 2) nonflammability and nonexplosiveness, 3) compatibility with soda lime, 4) pleasantness to the patient, 5) it can be given with other anesthetic agents, 6) diminished secretions, 7) diminished nausea and vomiting, and 8) rapid recovery.

Disadvantages include: 1) potency, 2) circulatory depression, 3) respiratory depression, 4) incomplete muscle relaxation except with deep anesthesia, 5) difficulty in assessing the depth of anesthesia, and 6) possible expense.

It will be noted that the potency of Fluothane is listed as both an advantage and disadvantage. This is done because this property of Fluothane is a two-edged sword. It enables the anesthetist not only to use it to produce all planes of anesthesia, but also to quickly and smoothly deepen the anesthesia should it be inadequate for the surgical procedure. On the other hand, its potency can be a liability as considerable depth of anesthesia can be rapidly attained inadvertently with resultant dangerous depression of the circulatory and respiratory systems. Since the degree of depression appears to be directly related to depth of anesthesia and to concentration of Fluothane vapor it is felt that preferably

this agent should be given with vaporizers that will deliver a known concentration of vapor at known flow rates. This could be done either by calibration of existing ether vaporizers or by use of vaporizers specifically designed for Fluothane. Although the majority of our cases were done without calibrated vaporizers it is believed that their use is definitely to be preferred. This would be especially true if Fluothane were used by those who are not familiar with it. Use with a calibrated vaporizer and either semi-closed or non-rebreathing technics should give the widest margin of safety. This impression receives confirmation by Chang [2] who has reported the incidence of hypotension to be less when the semi-closed technic is compared to the closed circuit.

The mechanism of circulatory depression is still not clear. Conflicting evidence is presented by Severinghouse,[7] who feels that it is mainly a direct depressant effect on the heart, and by Burn *et al.*[1] who feel that it is principally due to direct depression of the central vasomotor center.

The depressant effect of Fluothane on respiration, while undesirable, is not an insurmountable drawback. In fact, where controlled respirations are desired, as in open chest operations, this property can work to the anesthetist's advantage. All of our present anesthetics depress respiration to some extent so that constant evaluation of the adequacy of ventilation should be as routine as that of cardiac action. To avoid deeper planes of anesthesia than are necessary, care must be taken when assisting or controlling respirations, and in most instances the percentage of vapor delivered to the patient will have to be reduced.

The lack of secretions with Fluothane, and its apparent salutary effect upon asthmatics may indicate a potential special usefulness for this agent in chest surgery and in any patient with a history of asthma who requires a general anesthetic.

The use of atropine as premedication or during the operation appears to protect the heart against the bradycardia often seen in deeper planes of anesthesia. This may tend to minimize the incidence of hypotension both during induction and maintenance and permit higher concentrations of Fluothane to be given with greater safety.

The incompleteness of muscle relaxation in most cases probably indicates that when Fluothane is used for intra-abdominal surgery, or other procedures requiring marked relaxation, one of the muscle relaxants will have to be used in addition to avoid the chance of circulatory depression seen with deeper planes of anesthesia.

The results of the liver function tests performed on 14 patients indicate that so long as hypoxia is avoided Fluothane does not damage hepatic function sufficiently to be recognized by present methods of measurement.

Probably with our present knowledge Fluothane is not well suited for the occasional anesthetist or for those unfamiliar with the technics of modern general anesthesia. As when any anesthetic is given, the facilities for immediate resuscitation must be available.

At present, it appears that Fluothane's main usefulness will be when a non-explosive anesthetic agent is necessary. With the increasing use of electronic monitoring devices this is becoming more and more a desirable property. Also, it may find a use as an anesthetic for minor surgical procedures on out-patients as it appears to combine a rapid return of consciousness with minimal after effects. Other indications for its use will probably appear with further study.

Summary

Clinical observations of 500 surgical procedures using Fluothane as the principal anesthetic agent have been reported. Its principal advantages and disadvantages have been listed. Suggestions as to its method of administration are given. From

these observations, it is felt that Fluothane will probably find a place in the anesthesiologist's armamentarium.

References

1. Burn, J. H., H. G. Epstein, G. A. Feigan and W. D. M. Paton: Some Pharmacological Actions of Fluothane. Brit. Med. J., 479, 1957.
2. Chang, J., H. H. Macartney and H. B. Graves: Clinical Experience with Fluothane, a New Non-Explosive Anaesthetic Agent. Canad. Anaesth. Soc. J., **4**:187, 1957.
3. Fairlie, C. W., T. P. Barss, A. B. French, C. M. Jones and H. K. Beecher: A Comparison of the Effects of Certain Anesthetic Agents on the Normal Liver. New Eng. J. Med., **244**: 615, 1951.
4. Johnstone, M.: The Human Cardiovascular Response to Fluothane Anaesthesia. Brit. J. Anaestht., **28**:392, 1956.
5. Little, D. M., Jr. and C. M. Barbour, Jr.: Hepatic Function Following Fluothane Anesthesia. Presented at the American Society of Anesthesiologists Convention, Oct. 14–18, 1957, Los Angeles, California.
6. Raventos, J.: The Action of Fluothane: A New Volatile Anesthetic. Brit. J. Pharmacol., **11**: 394, 1956.
7. Severinghaus, J. W.: Myocardial Depression with Fluothane in Man Studied by Chemical Sympathectomy. Presented at the American Society of Anesthesiologists Convention, Oct. 14–18, 1957, Los Angeles, Calif.
8. Stephen, C. R., D. C. Grosskreutz, J. H. A. Lawrence, L. W. Fabian, M. Bourgeois-Gavardin and J. Coughlin: Evaluation of Fluothane for Clinical Anaesthesia. Canad. Anaesth. Soc. J., **4**:246, 1957.