TRIFLUOROETHYLVINYL ETHER (FLUOROMAR®). I. PRELIMINARY CLINICAL AND LABORATORY STUDIES

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THE observation that fluorination lowers the flammability of aliphatic ethers has instigated an intensive investigation of these compounds, especially their anesthetic properties. Although fluorination diminishes anesthetic activity so that the fully fluorinated ether, perfluoroethyl ether, has been shown to be devoid of any anesthetic property, the compound trifluoroethylvinyl ether (Fluoromar®) has been found to exhibit promising anesthetic activity.

Trifluoroethylvinyl ether ($CF_3CH_2OCH=CH_2$) was first prepared by Shukys (1) in 1951 by reaction of acetylene ($CH\equiv CH$) and trifluoroethanol (CF_3CH_2OH). The trifluorocarbon configuration (CF_3—) of this ether is very stable and can be disrupted only with difficulty—for example, by fusion with alkali or treatment with a molten alkali metal. This compound has none of the chemical properties of inorganic fluorides, such as formation of the insoluble calcium fluoride and reaction with silica to form fluosilicates.

It is known that vinyl ethers tend to hydrolyze to form acetaldehyde. Krantz *et al.* (2) showed that Fluoromar did not hydrolyze in buffered solutions between pH 2.0 and pH 11.0 when incubated at 38 C. for three hours. Tests conducted by Greene (3) demonstrated that no acetaldehyde was formed after circulating synthetic respiratory gas mixtures of Fluoromar, oxygen, carbon dioxide and water vapor over soda lime maintained at temperatures between 70 and 100 C., thus indicating little or no tendency to hydrolyze. Analysis of the soda lime used in these tests showed that it contained no fluoride, thus indicating the stability of the carbon-fluorine bonds in Fluoromar. Its value as an inhalation anesthetic agent was studied by Krantz (2) in laboratory animals who showed it to have an anesthetic potency equal to ethyl ether and to be relatively nontoxic.

The present studies were undertaken with the following objectives: (1) to obtain data on blood and alveolar concentrations of Fluoromar sufficient to arrive at the different stages and planes of anesthesia as

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described by Guedel (4), (2) to correlate clinical and laboratory data on Fluoromar, and (3) to gain some insight into the usefulness and limitations of this new agent.

MATERIALS AND METHODS

Materials.—The patients employed in this study were unselected. The operative procedures were varied and included both major and minor categories. Some subjects were volunteers (table 1).

TABLE 1

OPERATIVE PROCEDURES

Region	No.
Head and neck	7
Thorax	15
Abdominal	32
Rectovaginal	15
Extremities and plastic	12
Volunteers	8
Total	89

Ages of the subjects ranged from 3 months to 72 years. Sixty-seven subjects were females, 20 males. The predominance of female patients may be ascribed to the availability of these patients in relation to time of operation and the convenient proximity of the ward to the operating rooms and the laboratory where the analyses were performed. Several volunteers were subjected to Fluoromar anesthesia for purposes of correlating anesthesia and analgesia levels with blood concentrations under better controlled conditions than during an operation.

Methods.—Fluoromar was administered by vaporizing from the unmodified ether vaporizers of various anesthesia machines such as the Heidbrink, the Chicago Anesthesia, and the Foregger machines. Different techniques were employed, for example, open, semi-open, semi-closed, and closed, utilizing either the circle or the to-and-fro. A "cyprane" inhaler was used in some cases for analgesia studies. An orotracheal tube was inserted in the majority of cases, although an occasional nasotracheal tube was utilized. For induction, a face mask was employed.

In most of the cases, Fluoromar was used as the sole anesthetic agent for induction and maintenance. In some cases it was utilized in conjunction with nitrous oxide or thiopental. Curare and curariform agents were employed in some instances to facilitate endotracheal intubation where time was at a premium. It was also used to aid relaxation especially in abdominal operations. The curare agents employed were dimethyl-*d*-tubocurarine or succinylcholine. Preoperative medication was limited to two drugs, meperidine and scopolamine. A few cases were done without preoperative medication. The stages

and planes of anesthesia were judged insofar as possible with reference to the signs of anesthesia as described by Guedel (4).

PROCEDURE

Venous blood samples for analysis were obtained from the veins of the arm or hand, or occasionally from the leg or foot veins, during each of the planes of anesthesia as determined by the person administering the anesthetic with one or two of the senior staff and during the recovery period. Twenty cubic centimeters of blood was drawn into a syringe previously wet with heparin.

Gas samples were taken in 60 cc. gas sampling flasks with stopcocks at both ends. Whenever an endotracheal tube was in place, a no. 14 French urethral catheter was passed through the side arm of a Rovenstine elbow connector through the tracheal tube to the estimated level of the carina. The exposed end of the catheter was connected to the gas sampling flask and approximately ten times the volume of the flask was aspirated by means of a rubber bulb. The aspirations were timed to coincide as nearly as possible with the end of the patient's exhalation.

Samples for quantitative analysis were then introduced into the analysis apparatus as rapidly as possible, usually within two to three minutes. The blood samples were analyzed by steam distilling the Fluoromar into an excess of standard bromine solution, the excess then being determined iodometrically. The gas samples were analyzed by forcing the contents of the gas flasks through standard bromine and concluding the analysis in a similar manner. The analytical reaction is as follows:

$$CF_3CH_2OCH=CH_2 + Br_2 \rightarrow CF_3CH_2OCHBr\text{–}CH_2Br$$

One molecule of bromine adds to the double bond of each molecule of Fluoromar ; thus the amount of bromine which reacts is in direct proportion to the Fluoromar originally present.*

Liver function tests (bromsulfalein and thymol turbidity) were performed on 18 patients before and twenty-four hours after anesthesia.† Positive clinical observations were noted and recorded if significant.

RESULTS

The results of the chemical analyses of blood and respired gases for Fluoromar are presented in table 2, and illustrated graphically in figures 1 and 2.

The data have been treated statistically to determine the 95 per cent confidence limits of the mean values ($\bar{x} \pm a_{95}\,\sigma$, $P=0.95$) and to test

* Details of analysis will be presented in another paper by Harry W. Linde.
† These are the initial results of organ-function studies being done.

TABLE 2

FLUOROMAR® ANESTHESIA AND ANALGESIA

	Blood Conc. mg.%[a]	No. of Analyses	Respired Gas Conc. vol.%[a]	No. of Analyses
Analgesia	7.7 ± 10.4[b]	3	2.0 ± 1.2[c]	6
Plane 1	17.4 ± 3.5[b]	25	3.2 ± 1.3[c]	15
Plane 2	25.4 ± 3.1	21	5.0 ± 1.2	15
Plane 3	38.2 ± 5.6[d]	14	8.2 ± 1.8	6
Plane 4	42.4 ± 12.4[d]	8	12.9 ± 2.6	4
Postoperative				
35 min.	10.5 ± 6.4	2		
1 hour	3.9 ± 1.9	10		
2 hours	0.9 ± 0.7	7		
3 hours	0	1		

[a] The values given are the mean and the range of the 95% confidence limits ($P = 0.95$), $\bar{x} \pm a_{95}\,\sigma$, based on Student's t.

[b,c,d] These pairs of mean values do not differ from one another significantly ($P = 0.05$, t-test). All other data do differ at the 0.05 level.

the significance of the difference between mean values for the various planes ($P = 0.05$) by Student's t-test. It will be noted in table 2, for instance, that the observed gas concentrations in analgesia and first plane anesthesia do not seem to show a marked difference. In figures 1 and 2 the vertical lines above and below the points represent the 95 per cent confidence limits of the mean values. As might be expected, figure 1 shows that increasing concentration of the agent in the respired

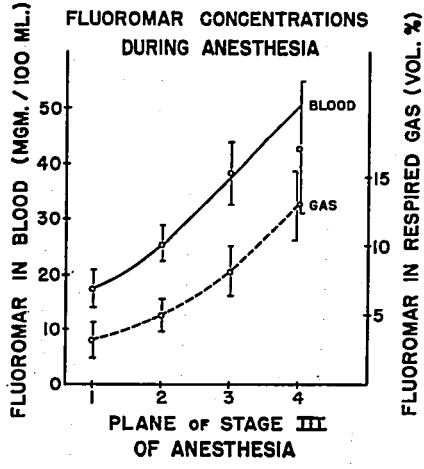

FIG. 1. Fluoromar® concentrations in blood and respired gases during anesthesia.

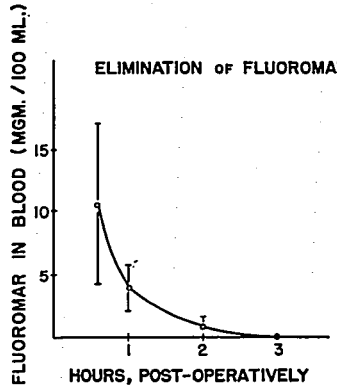

FIG. 2. Fluoromar® concentrations in blood in the postoperative period.

gases causes a proportionate increase of the agent in the venous blood. In fact, in the first three planes of Stage III, the ratio of the concentration of Fluoromar in the respired gases (in mg./100 ml. of gas) to that in the venous blood (in mg./100 ml. of blood) is relatively constant, being 0.91, 0.97, and 1.04, respectively. The elimination of Fluoromar from the body as shown by its decreasing concentration in the venous blood is shown graphically in figure 2. After one hour the Fluoromar level in the blood is well below that for analgesia or first plane anesthesia, a fact confirmed by clinical observation.

Fluoromar anesthesia preceded by induction with nitrous oxide seems to indicate need for smaller amounts of Fluoromar to maintain anesthesia (table 3). The blood levels in the third plane of this group differ significantly ($P = 0.01$) from blood levels of third plane Fluoromar induced and maintained anesthesia. Induction with intravenous thiopental diminishes significantly ($P = 0.05$) the quantity of Fluoromar required to maintain anesthesia in all planes (table 4).

TABLE 3

FLUOROMAR® ANESTHESIA AFTER NITROUS OXIDE INDUCTION

	Blood Conc. mg.%	No. of Analyses	Respired Gas Conc. vol.%	No. of Analyses
Plane 1	11.2 ± 4.8^a	6	4.4 ± 1.6^b	4
Plane 2	19.9 ± 6.9^a	8	$4.3 \pm 9.8^{b,c}$	2
Plane 3	28.9 ± 3.9	7	8.2 ± 3.2^c	5

[a] These data do not differ significantly ($P = 0.05$) from the corresponding data for Fluoromar as the sole anesthetic.

[b,c] Values do not differ significantly from one another ($P = 0.05$).

TABLE 4

FLUOROMAR® ANESTHESIA AFTER SODIUM PENTOTHAL® INDUCTION

	Blood Conc. mg.%*	No. of Analyses	Respired Gas Conc. vol.%	No. of Analyses
Plane 1	14[a]	1	2.2[c]	1
Plane 2	14.4 ± 6.7[a,b]	5	2.9 ± 5.1[c,d]	2
Plane 3	20.7 ± 3.8[b]	6	5.5 ± 3.1[d]	3

* These blood concentrations all differ significantly from the corresponding data for Fluoromar as the sole anesthetic agent ($P = 0.05$).

[a,b,c,d] Values do not differ significantly from one another ($P = 0.05$).

Liver function tests as obtained in 18 cases are shown in table 5. Complications as observed during anesthesia were classified according to degree of severity and time of occurrence (table 6).

TABLE 5

LIVER FUNCTION TEST–BROMSULFALEIN *

No. of Cases	% Retention	Interpretation
14	0– 4.1	Within normal
2	7.2– 8.5	Slight
2	13.6–25.5	Moderate
18		

* BSP given—5 mg./Kg. of body weight. Thymol turbidity tests done simultaneously showed no significant changes.

DISCUSSION

The data obtained from analyses of blood and respiratory gas levels show close correlation. Surgical anesthesia (planes 1, 2 and 3, Stage III) was achieved with blood levels of 17 to 38 mg. per cent and alveolar gas levels of 3.2 to 8.2 volumes per cent. In spite of unfamiliarity with the drug, determination of planes of anesthesia by different individuals was rather consistent, as witness the narrow variation in the blood and

TABLE 6

COMPLICATIONS

	No. Cases			Time
	Mild	Moderate	Marked	
Excitement	26	11	4	Induction
Salivation	9	6		Induction
Hypotension	4		1*	Maintenance
Bradycardia		2		Maintenance
Auricular fibrillation			1†	Postoperative
Nausea	4			Postoperative
Vomiting	7	3		Postoperative

* Immediately after removal of a large ovarian cyst.

† Presence of preoperative cardiac pathology.

gas levels obtained (see table 2, especially of planes 1 to 3). The wide variation seen in plane 4 may be ascribed to the fact that samples were obtained with the subjects on the verge of apnea or of just having gone into apnea. Tidal exchange at this point was so poor that respiration was invariably assisted. Of course, deep anesthesia was also intentionally provoked by means of assisting respiration.

Judging from the gas and blood levels necessary to achieve surgical anesthesia, the drug is quite potent. Table 7 illustrates comparable levels with other agents. Initial studies by Krantz *et al.* (2) in lab-

TABLE 7

PROPERTIES OF FLUOROMAR® AND OTHER AGENTS

Property	Trifluoroethyl Vinyl Ether CF_3CH_2 O $CH_2=CH$	Ethyl Vinyl Ether CH_3CH_2 O $CH_2=CH$	Divinyl Ether $CH_2=CH$ O $CH_2=CH$	Diethyl Ether CH_3CH_2 O CH_3CH_2	Cyclopropane $(CH_2)_3$
Boiling point, C.	42.7	35.8	28.4	34.6	−32.9
Vapor pressure, mm. Hg					
at 20 C.	295[5]	428[5]	553[7]	442[5]	75 psi[9]
at 40 C.	670[5]		1145[7]	921[5]	
Specific gravity 20 C.	1.13	0.76	0.77	0.71	—
Calc. gas density (air = 1)	4.4	2.5	2.4	2.6	1.5
Lower flammability limit in:[10]					
O_2	4.0%	2.2%	1.9%	2.0%	2.5[11]
Air	4.2		1.7	1.9	
75% O_2–25% N_2O	4.0				
Minimum spark ignition energy, millijoules (10)					
for 3% of vapor in dry O_2	—	high		0.39	4.0[12]
4%	—	0.13		0.05	0.2
6%	0.30	0.02		0.01	0.01
8%	0.08	0.01		0.01	0.003
Partition coefficient (Gb/Ga)	5.00*		7–10	15.00	0.3–0.2
Solubility in Water, ml./100 ml.	0.4[13]	0.8[14]	0.7[12]	8.0[12]	0.04[12]
Oil/H_2O ratio at 37.5 C	91 (23 C)[14]	45[15]	41[9]	3.2[9]	34[9]
Oil/Blood ratio at 37.5 C				3.3[9]	15[9]
Gas concentration for surgical anesthesia, volumes %	3.2–8.2*		4[9]	3–10[16]	7–23[16]
Blood concentration for surgical anesthesia, mg.%	17–38*	about 25†	30–40[9]	50–150[16]	2.5–17[16]

* This study.
† Preliminary Unpublished Results, Sadove, Balagot and Linde, 1955.

oratory animals prompted him to state equal potency between this drug and diethyl ether. Physical properties exhibited by this drug do not approximate that of diethyl ether. It is poorly soluble in water, 0.4/100 ml., as compared to 8/100 ml. for ethyl ether. Its vapor pressure is much lower than ethyl ether. Its oil/water partition coefficient is extremely high—higher than chloroform and cyclopropane.

In spite of these apparent deficiencies, there must be some basis for the unequivocal statement made by Krantz that it equalled ethyl ether in anesthetic potency. It is possible that its high oil-water partition coefficient, indicating affinity for lipoids, might offer an explanation. The final arbiter of narcotic potency is the nerve cell, and its lipoid content is about 18 per cent. The low vapor pressure (295 mm. Hg at 20 C.) and its low solubility in water may explain the prolonged induction period observed by Krantz and demonstrated clinically. Although it is poorly soluble in water, its partition coefficient (ratio of blood concentration to alveolar concentration) is about 5. Probably the red cells in the blood carry a greater amount of the agent than the plasma. Attempts were made to demonstrate such in the laboratory, but technical difficulties were insurmountable at that time.

Thiopental induction prior to Fluoromar administration diminished the amount of Fluoromar necessary to achieve surgical anesthesia. The same seemed to be true with the initial administration of nitrous oxide. These observations are incidental but interesting. No explanations are offered except a possible additive action.

Orth and Dornette (17) employed Fluoromar in 40 cases and made the following observations: (1) the induction period was found to be one to two minutes in infants and two to four minutes in adults; (2) recovery time was one to two minutes; (3) analgesia was excellent. Krantz, in anesthetizing one of us (MSS), observed a short induction period with a smooth and uneventful recovery. These two clinical observations, especially as regards induction period, seem to be inconsistent with laboratory and clinical observations in this study that induction was somewhat prolonged. The inconsistency is more apparent than real. If induction is taken to imply loss of consciousness, then induction as far as Fluoromar is concerned is rapid—falling within Dornette's range of one to four minutes. On the other hand, if induction is taken to encompass the time loss of consciousness is observed, to the time surgical anesthesia is achieved, then induction is prolonged. An excitement stage occasionally supervenes during this period.

Excellent analgesia, as pointed out by Orth and Dornette, was observed in this study and was quite impressive. This observation prompted trial administration of this agent with the "cyprane" inhaler. Blood levels were obtained and these corresponded with blood levels taken during recovery from anesthesia—the patient was con-

scious but demonstrated marked analgesia as shown by indifference to or no pain upon venipuncture for blood samples.

COMPLICATIONS

In this preliminary study, the drug appears to be relatively safe. Complications were few and mild (table 6). As observed by Krantz (2) in the laboratory, the heart and the blood pressures were not affected to a significant degree by the agent. One patient developed auricular fibrillation postoperatively, but this patient had had previous bouts of auricular fibrillation. Absence of nausea and vomiting was the rule rather than the exception. Liver function tests on 18 patients (table 5) showed slight to moderate retention of bromsulfalein in 4 patients. These data compare favorably with studies on other agents, for example, ether and spinal anesthesia (18). Thymol turbidity tests done simultaneously showed no impressive changes.

One of the observations that actuated the development of this agent was the possibility of obtaining a vapor that was less flammable as compared to other anesthetic agents such as ethyl ether and cyclopropane. This has been accomplished (table 7), but the fact remains that it is still flammable within its anesthetic range, though to a much lesser degree.

SUMMARY AND CONCLUSIONS

Data have been presented to show studies on a new anesthetic agent Fluoromar. Blood level studies show that surgical anesthesia can be achieved with 17 to 38 mg./100 ml., and alveolar gas levels of 3.2 to 8.2 volumes per cent. The drug produces a good analgesic state. Unconsciousness is very quickly reached (one to four minutes), but the development of surgical anesthesia after unconsciousness is induced seems to be similar to ethyl ether—that is, relatively prolonged.

Clinically Fluoromar induces minimal anesthetic complications and conveys the impression of relative safety plus sufficient anesthetic potency.

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