

OBSERVATIONS ON TRIFLUOROETHYLVINYL ETHER

JOHN W. DUNDEE, M.D., HARRY W. LINDE, PH.D.
ROBERT D. DRIPPS, M.D.

STUDIES of partially fluorinated ethers by Krantz and colleagues (1, 2) suggested that trifluoroethylvinyl ether (Fluoromar®) might be a useful anesthetic agent. Its chemical relationship to other anesthetic ethers is shown in figure 1. This paper reports observations made during 300 administrations of trifluoroethylvinyl ether to surgical patients.

CLINICAL MATERIAL

Details of the operations performed, the duration of anesthesia, and the age, sex, and physical status of the patients are given in tables 1, 2, and 3. All anesthetic techniques applicable to diethyl and divinyl ethers were used in this study. The experience of the anesthetists ranged from medical students to senior consultants.

Diethyl ether	$\text{CH}_3\text{—CH}_2\text{—O—CH}_2\text{—CH}_3$
Divinyl ether (Vinethene®)	$\text{CH}_2\text{=CH—O—CH=CH}_2$
Ethylvinyl ether (Vinamar®)	$\text{CH}_3\text{—CH}_2\text{—O—CH=CH}_2$
Trifluoroethylvinyl ether (Fluoromar®)	$\text{CF}_3\text{—CH}_2\text{—O—CH=CH}_2$

FIG. 1. The formulas of trifluoroethylvinyl and other ethers.

The data for comparative studies were taken from records of 614 administrations of diethyl ether and 115 administrations of divinyl ether from all the administrations of these drugs at the University Hospital during 1954. As with trifluoroethylvinyl ether, these anesthetics were given by personnel with varying degrees of experience, and a large variety of operations were included.

OBSERVATIONS

Induction.—It was apparent almost at once that trifluoroethylvinyl ether was unsatisfactory for administration by the open drop method. Inductions were slow in 20 per cent of the cases, in contrast to 4 per cent for divinyl ether given by the same technique. This is probably

Accepted for publication October 11, 1956. Drs. Dundee and Dripps are in the Department of Anesthesiology, Hospital of the University of Pennsylvania and the University of Pennsylvania Schools of Medicine, Philadelphia, Pennsylvania. Dr. Linde is Senior Chemist, Research Laboratories, Ohio Chemical and Surgical Equipment Company, Murray Hill, New Jersey. This work was supported (in part) by grants from the Ohio Chemical and Surgical Equipment Company and the National Heart Institute, Public Health Service.

attributable to the higher boiling point of trifluoroethylvinyl ether, 42.7 C. compared to 28.4 C. for divinyl ether.

Trifluoroethylvinyl ether, however, could be easily introduced into a closed, or semiclosed system following nitrous oxide-oxygen. Probably because of its low solubility in water, 0.4 cc. per cent development of anesthesia was prompt.

Maintenance.—Again probably as the result of its low water solubility, trifluoroethylvinyl ether appeared to require considerable care and attention in order to achieve maintenance of a constant plane of anesthesia. Changes in depth of anesthesia occurred with extraordi-

TABLE 1
NATURE OF OPERATIONS

General Surgery		45
Upper abdominal	7	
Hernias	3	
Surface operations	35	
Gynecology		173
Abdominal operations	69	
Perineal operations, major	20	
Perineal operations, minor	75	
Urology		20
Abdominal operations	2	
Endoscopy, major	4	
Endoscopy, minor	14	
Orthopedics		29
Major operations	25	
Minor operations	4	
Otolaryngology		8
Major operations	4	
Minor operations	4	
Dental Extractions		23
Obstetrics		2
	<hr/>	
Total		300

nary rapidity. This flexibility was useful if anesthesia had become inadequate, but was also occasionally embarrassing since apnea could readily be reached. In the latter instance, if administration of the drug were discontinued, spontaneous respiration was usually re-established quickly (fig. 2).

Signs of Anesthesia.—The signs and stages of anesthesia, described by Guedel were frequently inapplicable to trifluoroethylvinyl ether. Especially after an opiate as preoperative medication, respiratory paralysis might appear (Guedel: plane 3) before complete cessation of eyeball movement (Guedel: plane 1). The pharyngeal reflexes were not always obtunded before the onset of respiratory paralysis, and it was not unusual to hear laryngeal stridor or have a patient cough when other signs suggested deep surgical anesthesia.

TABLE 2
DURATION OF ANESTHESIA

Duration of Anesthesia	Number of Patients
Under 15 minutes	38
15-30 minutes	74
31-60 minutes	52
61-120 minutes	57
121-180 minutes	55
181 minutes and over	24

Electroencephalographic Changes.—Patterns of electroencephalographic changes similar to those described for diethyl ether (3) could usually be observed with trifluoroethylvinyl ether, but once surgical anesthesia was established, some difficulty was encountered in using the tracing as a means of assessing the depth of anesthesia. Observation in 12 subjects showed that surgical anesthesia occurred at levels 2-3 and that levels 4-5 generally indicated deep anesthesia. Apnea occurred between levels 5-7; in one subject spontaneous respiration persisted in the absence of electrical activity, while in others the respiratory exchange became inadequate at level 5.

Blood Levels.—Arterial blood trifluoroethylvinyl ether levels were determined on 22 subjects (table 4) and, as would be expected, progressive depression of the nervous system accompanied increasing blood concentrations of the drug.

Respiration.—The effects of trifluoroethylvinyl ether on respiratory tidal volume and respiratory rate will be the subject of a separate communication, and only the more important findings of this study will be mentioned.

Trifluoroethylvinyl ether appeared to be a profound respiratory depressant in deeper planes of anesthesia. In patients who were not

TABLE 3
DETAILS OF PATIENTS

	Number of Patients
Age	
Under 5 years	14
5-10 years	22
11-20 years	26
21-40 years	109
41-60 years	106
61-80 years	22
81 years and over	1
Sex	
Female	240
Male	60
Physical Status	
One	104
Two	87
Three	19

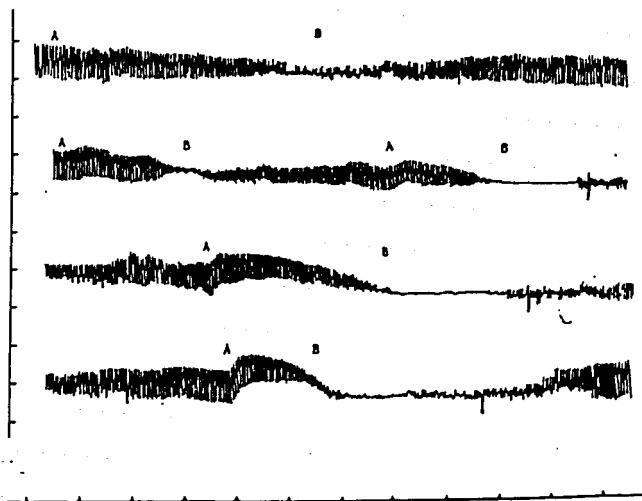


FIG. 2. Continuous spirometry tracing, showing ease with which anesthesia can be deepened or lightened with trifluoroethylvinyl ether. At (A) the Heidbrink vaporizer was set at 7, and at (B) the vaporizer was removed from the circuit. The system was not flushed with oxygen during the period of this observation. Average blood pressure at (A) was 150/77, and at (B) 100/60. Abscissa shows time intervals of one minute and ordinate shows ventilation of 500 cc.

TABLE 4
ARTERIAL BLOOD TRIFLUOROETHYLVINYL ETHER LEVELS*

Depth of Anesthesia	Number of Readings	Blood Trifluoroethylvinyl Ether Level (mg. %)		
		Average	Standard Deviation	Range
Surgical Anesthesia†				
Plane 1	12	14.6 ± 0.77	2.65	10.8-20.0
Plane 2	17	20.4 ± 1.35	5.57	12.1-31.5
Plane 3	19	28.5 ± 1.08	4.69	18.7-34.7
Plane 4	7	38.7 ± 2.88	7.62	33.0-50.0
Apnea‡	6	49.3 ± 1.62	6.56	40.3-61.0

* Atropine only as preoperative medication.

† Thirteen readings where it was impossible to decide the exact depth of anesthesia are included in two columns, e.g., a blood level obtained at the junction of plane 3 and 4 would be included above in both planes.

‡ Four of these cases had minimal respiratory excursions in plane 4 of surgical anesthesia. Spontaneous apnea was not allowed to occur, but the gas concentration of trifluoroethylvinyl ether was maintained for five minutes with controlled respiration.

given an opiate as preoperative medication trifluoroethylvinyl ether frequently caused tachypnea. The respiratory rate increased with the duration and depth of anesthesia, but once tachypnea was established the rate could be quickly reduced by the intravenous injection of 10-20 mg. meperidine. Tidal volume was markedly depressed at high respiratory rates and acidosis followed prolonged tachypnea.

Cardiovascular System.—In one quarter of the cases in this series there was evidence of a depressant effect of trifluoroethylvinyl ether on the cardiovascular system following prolonged or deep anesthesia. In six instances the decrease in systolic blood pressure exceeded 40 mm. of Hg for a period of more than five minutes (maximum fall 140/100 to 60/25). The effect of the depth of anesthesia on the mean blood

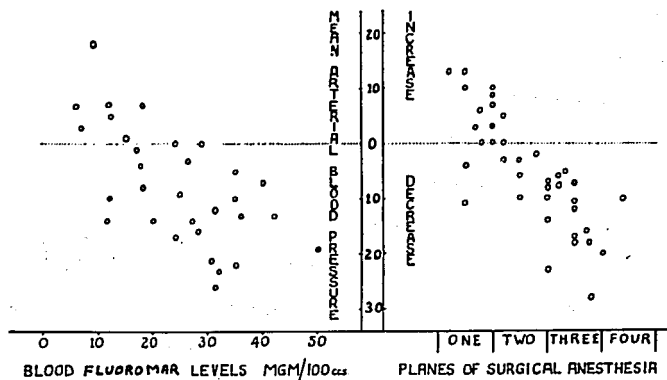


FIG. 3. Relationship of mean arterial blood pressure to trifluoroethylvinyl ether content of arterial blood and depth of anesthesia as judged clinically.

pressure is shown in figure 3, where changes from the preoperative reading are correlated with arterial blood levels of trifluoroethylvinyl ether in 17 patients and with the clinical estimation of the depth of anesthesia in 27 cases.

Continuous electrocardiographic studies (with 3 limb leads) were completed on 11 patients for periods varying from 25 to 185 minutes and with depths of anesthesia varying from electroencephalographic levels 2 to 7. A normal tracing was found in 4 cases and 3 patients had tachycardia during deep anesthesia. A transient displacement of the pacemaker, as shown by P wave changes or A-V nodal rhythm, occurred in three cases during light anesthesia, but returned to normal when anesthesia was deepened. The only marked abnormality was a temporary inversion of the T wave in lead II in one patient during very deep anesthesia.

Muscular Relaxation.—Relaxation of jaw muscles appeared to be more difficult to attain than relaxation of the abdominal wall.

Recovery.—Recovery from anesthesia occurred rapidly. Quantitative data supporting this belief was found in one patient whose blood trifluoroethylvinyl ether concentration decreased from 22.4 to 4.9 mg. per cent within eight minutes of removal of the face mask. Anesthesia had lasted 25 minutes. Recovery from electroencephalographic level 5 to level 1-2 was observed in four minutes after 30 minutes of anesthesia and from level 5-6 to level 2 in eight minutes after 180 minutes of anesthesia. In only five of the 280 cases was complete return of the mental faculties delayed for more than 30 minutes after the end of anesthesia.

Analgesia.—According to data supplied by the manufacturer, the lower limit of flammability of trifluoroethylvinyl ether is 4 per cent in oxygen and in 75 per cent N₂O in oxygen. Sadove, Balagot and Linde (4) reported that trifluoroethylvinyl ether was analgesic in inspired gas concentrations of 1.2-2.0 vol. per cent. It was decided therefore to add trifluoroethylvinyl ether to nitrous oxide-oxygen or to thiopental-nitrous oxide-oxygen when an explosive hazard existed and deep anesthesia was not required. In 9 consecutive cases the range of trifluoroethylvinyl ether in the inspired air was from 0.3 to 2.4 vol. per cent. The clinical impression was gained that the volatile liquid stabilized anesthesia and permitted a smoother course. This is of course difficult to measure. Trifluoroethylvinyl ether cannot be used for more than 8-10 minutes in the usual trichloroethylene inhaler. The heat of vaporization of the former is such that cooling of the inhaler prevents continued volatilization of the liquid.

Compatibility with Soda Lime.—Unlike trichloroethylene, trifluoroethylvinyl ether can be administered in closed systems. There is no chemical reaction involving the drug and any of the carbon dioxide absorbents.

DISCUSSION

The useful aspects of trifluoroethylvinyl ether include: (1) relatively low flammability, (2) compatibility with soda lime, (3) minimal incidence of cardiac arrhythmia, even with a challenging dose of epinephrine (5). (4) minimal blood solubility permitting rapid induction and recovery, (5) good analgesia, and (6) high degree of patient acceptability.

On the debit side can be listed: (1) low volatility, reducing its value in open drop techniques, (2) respiratory depression and respiratory acidosis in deeper planes of anesthesia, (3) tachypnea unless an opiate is used for preoperative medication, and (4) occasional difficulty with jaw relaxation.

It is impossible to predict the ultimate place of this substance in anesthesiology. In our clinical practice it is being used in low concen-

trations in the presence of explosive hazards and for procedures which require only first or upper second plane anesthesia. It thus has found application in dental surgery, orthopedics, and certain types of gynecological, urologic and general surgery. If some of the clinical impressions outlined in this and other papers can be substantiated, trifluoroethylvinyl ether may prove to be a useful anesthetic agent.

SUMMARY

Observations during 300 administrations of trifluoroethylvinyl ether have been reported. The advantages and disadvantages of trifluoroethylvinyl ether as an anesthetic agent have been compared with those of diethyl ether and divinyl ether. From the clinical impressions it appears that trifluoroethylvinyl ether deserves further study as a useful anesthetic agent.

REFERENCES

1. Lu, G., Ling, S. J., and Krantz, J. C., Jr.: Anesthesia; Anesthetic Properties of Certain Fluorinated Hydrocarbons and Ethers, *ANESTHESIOLOGY* 14: 466 (Sept.) 1953.
2. Krantz, J. C., Jr., Carr, J., Lu, G., and Bell, F. K.: Anesthesia; Anesthetic Action of Trifluoroethylvinyl Ether, *J. Pharmacol. & Exper. Therap.* 108: 485 (Aug.) 1953.
3. Courtin, R. F., Bickford, R. G., and Faulconer, A., Jr.: Classification and Significance of Electro-encephalographic Patterns Produced by Nitrous Oxide-Ether Anesthesia During Surgical Operation, *Proc. Staff Meet. Mayo Clin.* 25: 197 (April 12) 1950.
4. Sadove, M. S., Balagot, R. C., and Linde, H. W.: Trifluoroethylvinyl Ether (Fluoromar); Preliminary Clinical and Laboratory Studies, *ANESTHESIOLOGY* 17: 591 (July-Aug.) 1956.
5. White, J. M., Jr., Nations, N., Stavney, L. S., and Morris, L. E.: Cardiac Conduction in Dog During Anesthesia with Fluoromar, *J. Pharmacol. & Exper. Therap.* 15: 499 (March) 1956.

AUSTRIAN-GERMAN-SWISS SOCIETIES OF ANAESTHESIOLOGISTS MEETING

The next joint meeting of the Austrian, German and Swiss Societies of Anaesthesiologists will be held in Vienna, June 13-15, 1957. The main topics will be "Postoperative Treatment." There will also be other scientific papers.

To assure accommodations participants are requested to contact Dr. K. Steinbereithner, I. Chirurgische Universitäts-Klinik, Wien IX., Alserstrasse 4, before January 15, 1957. Applications for papers should also be made to the same address, not later than February 28, 1957. All members of the American Society of Anesthesiologists are invited to attend.