ANESTHESIA. LI. A COMPARATIVE STUDY OF ETHYLVINYL AND TRIFLUOROETHYLVINYL ETHERS

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SEVERAL clinical studies with trifluoroethylvinyl ether (Fluoromar®) have appeared in the literature (1, 2). Since trifluoroethylvinyl ether is the 1,1,1,-trifluoroethyl analogue of ethylvinyl ether (Vinamar®), and each appears to be useful as an anesthetic agent (3, 4, 5), it was thought that a comparative study of the two compounds would prove interesting.

These studies embrace relative potency determinations of trifluoroethylvinyl and ethylvinyl ethers in the mouse, anesthetic indexes in the monkey, relative curarimimetic action in the dog, and respiratory effects under deep anesthesia.

METHODS

Anesthetic Potency.—These studies were carried out on mice placed in the anesthetic jar as shown in figure 1. The atmospheric pressure in the jar was reduced slightly and the precise volume of the anesthetic agent, previously vaporized by reduced pressure in the gas burette, introduced. A uniform temperature of 28 ± 0.5 C. was maintained in the jar. In each experiment 3 mice were exposed to the different concentrations of each of the anesthetic vapors. The mice were observed for a period of ten minutes. Those animals which became anesthetized within five minutes and remained in a state of anesthesia for the remainder of the observation period were included in the calculation of the AD_{50}. Those mice which developed respiratory arrest within five minutes were included in the calculation of the LD_{50}. For purposes of comparison, diethyl ether, U.S.P., was also included in these studies. Potencies and their statistical comparison were calculated by the method of Litchfield and Wilcoxon (6).

Anesthetic Index.—The anesthetic indexes of the two compounds were determined on a series of 4 Rhesus macacus monkeys using a technique previously described (7). Owing to the smaller size of the animals, volumes were reduced to one half of those used for dogs.

Curarimimetic Action.—Dogs anesthetized with a cyclopropane-oxygen mixture served as controls. Diethyl ether, trifluoroethylvinyl

Accepted for publication November 20, 1956. The authors are in the Department of Pharmacology, University of Maryland School of Medicine, Baltimore, Maryland. The work was supported by a research grant from the Ohio Chemical & Surgical Equipment Co. (Division of Air Reduction Company, Inc.), New York, New York.

ether, and ethylvinyl ether were given through a tracheal cannula after vaporization. Respiration was measured by a tambour connected to the tracheal cannula. The gastrocnemius muscle was exposed and the tendon freed at the distal end and connected to a muscle lever. The exposed sciatic nerve was severed and sectioned proximal to its passage into the leg. The leg was fixed by clamps at the distal end of the tibia. Control responses to the peripheral stimulation of the sciatic nerve by faradization (ten second duration) were carried out by means of a

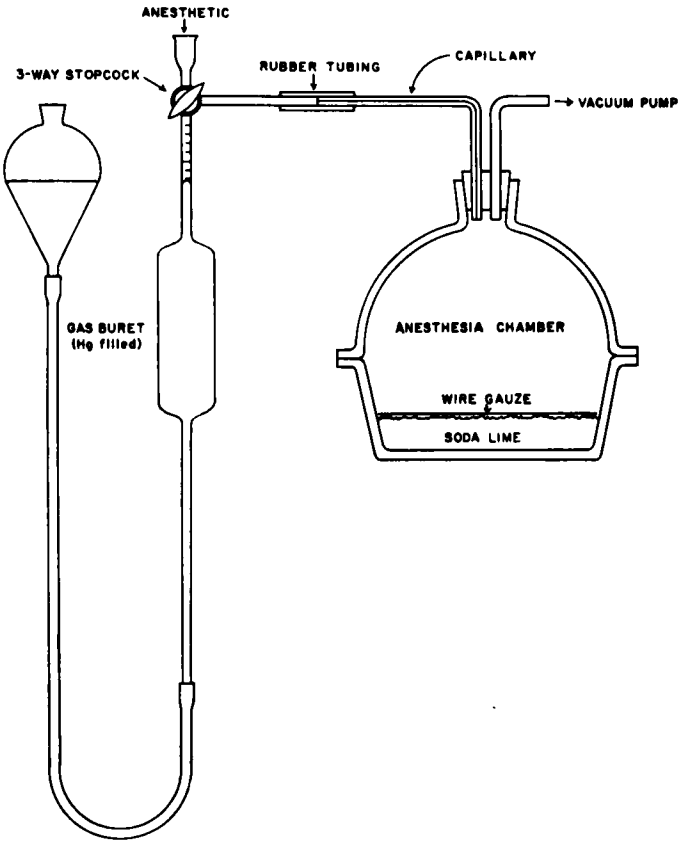

FIG. 1. Anesthetic chamber for mice.

Harvard inductorium until the maximal contraction became uniform. The anesthetic was then changed to diethyl ether, trifluoroethylvinyl ether or ethylvinyl ether, and the response determined at various anesthetic levels.

Respiratory Effects under Deep Anesthesia.—Control oxygen consumption determinations were carried out on monkeys using the Benedict-Roth respirometer. The animal was anesthetized by the anesthetic index procedure until an amount of agent had been administered that was 50 per cent of that previously required for respiratory arrest.

TABLE 1

ANESTHETIC POTENCIES (MICE)

	Ethylvinyl Ether		Trifluoroethylvinyl Ether		Diethyl Ether	
	AD_{50} Conc.	LD_{50} Conc.	AD_{50} Conc.	LD_{50} Conc.	AD_{50} Conc.	LD_{50} Conc.
ED_{50}	5.6%	16.5%	4.7%	12.7%	6.1%	16.2%
$f_{ED_{50}}$*	1.040	1.030	1.058	1.052	1.065	1.033
S†	1.102	1.050	1.287	1.105	1.148	1.060
f_S*	1.025	1.024	1.090	1.044	1.057	1.029
A.I.‡	2.95		2.73		2.66	
$f_{A.I.}$*	1.05		1.08		1.06	

* Error factor for 5 per cent probability ($p = 0.05$).
† Slope of dose-response line.
‡ Anesthetic index = LD_{50}/AD_{50}.

The oxygen consumption was again measured for a period of six minutes and anesthesia maintained by the administration of 0.25 cc. of the agent per minute.

RESULTS AND DISCUSSION

Anesthetic Potency.—The data on anesthetic potency and anesthetic index using 474 mice are shown in table 1. Their interpretation is in table 2. In testing the data for parallelism of effect of the three agents at various concentrations it was found that parallelism existed.

Trifluoroethylvinyl ether appears to be the most potent of the three anesthetics, followed by ethylvinyl ether and diethyl ether. Trifluoroethylvinyl ether produces respiratory arrest in lower concentrations than does diethyl ether or ethylvinyl ether. Statistically the anesthetic indexes are of the same order of magnitude. Our data on ethylvinyl ether are in close agreement with those of Mörch, Ayerigg,

TABLE 2

POTENCY RATIOS OF DATA IN TABLE 1

		P.R.	$f_{P.R.}$*	Conclusion
Ethylvinyl ether and diethyl ether	AD_{50}	1.085	1.08	Ethylvinyl ether is more potent
	LD_{50}	1.02	1.05	No difference
Ethylvinyl ether and Fluoromar	LD_{50}	1.30	1.08	Ethylvinyl ether is less toxic
Fluoromar and diethyl ether	LD_{50}	1.275	1.08	Trifluoroethylvinyl ether is more toxic
Ethylvinyl ether and diethyl ether	LD_{50}/AD_{50}	1.11	1.09	Ethylvinyl ether has greater anesthetic index
Ethylvinyl ether and Fluoromar	LD_{50}/AD_{50}	1.08	1.10	No difference
Fluoromar and diethyl ether	LD_{50}/AD_{50}	1.02	1.10	No difference

* Error factor for 5 per cent probability ($p = 0.05$).

and Berger (8), who found the concentrations required to produce surgical anesthesia and respiratory arrest in mice to be 6 and 16 volumes per cent, respectively.

Anesthetic Index.—The comparative data for ethylvinyl ether and trifluoroethylvinyl ether as measured by the anesthetic index technique on monkeys are shown in table 3.

TABLE 3

ANESTHETIC INDEX

Monkey Number and Sex	Weight (kg.)	Induction (cc./kg.)	Respiratory Failure (cc./kg.)	Anesthetic Index
Trifluoroethylvinyl ether				
1. M	3.25	0.23	0.69	3.0
	3.1	0.32	0.89	2.8
	3.1	0.32	0.81	2.5
2. F	5.3	0.24	0.75	3.2
3. F	2.6	0.48	1.44	3.0
	3.0	0.25	0.67	2.7
	3.0	0.25	1.00	4.0
	3.0	0.42	1.18	2.8
4. F	3.7	0.34	1.22	3.6
	3.7	0.34	1.15	3.4
Mean		0.32	0.98	3.1
S.D.		±0.07	±0.26	±0.45
Ethylvinyl ether				
1. M	3.25	0.38	1.77	4.6
	3.25	0.31	1.15	3.8
	3.1	0.24	0.73	3.0
2. F	5.3	0.33	1.18	3.6
	5.3	0.24	0.80	3.4
3. F	2.6	0.67	2.31	3.4
	2.6	0.38	1.15	3.0
	3.0	0.33	1.00	3.0
4. F	3.7	0.41	1.49	3.7
	3.7	0.41	1.35	3.3
Mean		0.37	1.29	3.5
S.D.		±0.12	±0.47	±0.50

Previously these same studies were conducted on dogs (4, 5). With ethylvinyl ether the anesthetic index was 3.00 and with trifluoroethylvinyl ether, 2.35. This confirms our findings with many anesthesias in dogs, namely, that the dog is more susceptible to respiratory arrest under anesthesia with trifluoroethylvinyl ether than the Rhesus monkey. In the monkey the anesthetic indexes of ethylvinyl ether and its

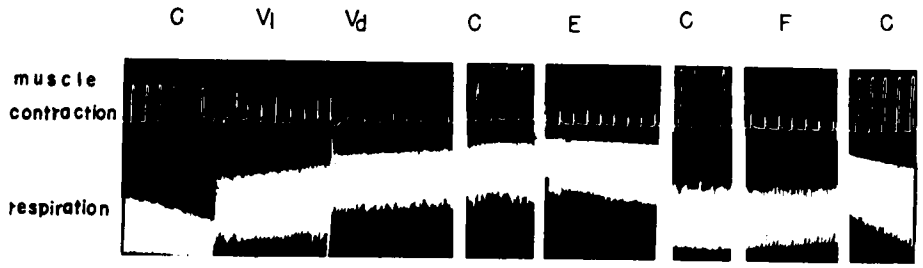

FIG. 2. Typical experiment illustrating the comparative curarimimetic action of trifluoroethylvinyl ether (dog). (C) Cyclopropane, (V) ethylvinyl ether, (l) light anesthesia, (d) deep anesthesia, (E) diethyl ether, (F) trifluoroethylvinyl ether.

trifluorinated analogue trifluoroethylvinyl ether are statistically the same.

Curarimimetic Action.—Each of the three anesthetic agents tested exhibited curarimimetic action. They varied, however, in the degree of this response. A typical experiment is shown in figure 2, and the data on the 8 dogs are shown graphically in figure 3.

Essentially these experiments show that the curarimimetic activity of diethyl ether, which has long been recognized, is paralleled by trifluoroethylvinyl ether in the dog, and to a limited degree by ethylvinyl ether.

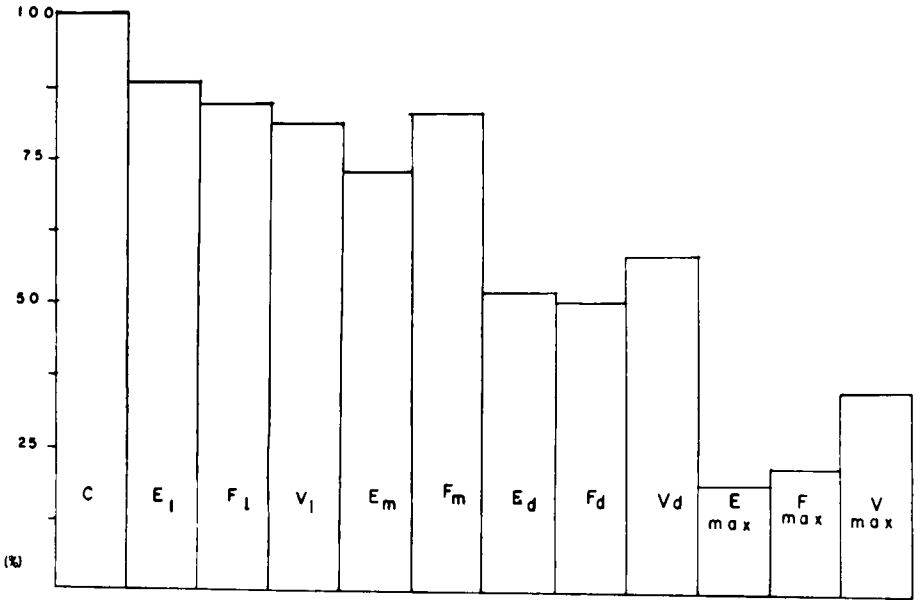

FIG. 3. Graphic representation of curarimimetic action of trifluoroethylvinyl, ethylvinyl and diethyl ethers (dog). (C) Cyclopropane, (E) diethyl ether, (F) trifluoroethylvinyl ether, (l) light anesthesia, (m) moderate anesthesia, (d) deep anesthesia, (max) maximum depression. Ordinate (%) = Average per cent of control concentration amplitude.

Respiratory Effect under Deep Anesthesia.—The data in table 4 show the effect of deep trifluoroethylvinyl ether and ethylvinyl ether anesthesia on the respiratory rate and oxygen consumption of the monkey. The percentage depression of oxygen consumption caused by the two agents is statistically the same. Ethylvinyl ether causes a significant increase in respiratory rate, which action is not shared by trifluoroethylvinyl ether. Two runs with diethyl ether anesthesia showed an average depression of oxygen consumption of 15.6 per cent.

TABLE 4

OXYGEN CONSUMPTION UNDER ANESTHESIA (MONKEY)

Monkey Number	Trial Number	Resp./min.	Cc./kg./hour	Resp./min.	Cc./kg./hour	Resp./min.	Cc./kg./hour
		Control		Trifluoroethylvinyl Ether		Difference	
1. F	1	44	3,481	45	3,267	+1	−214
	2	49	3,437	61	3,090	+12	−347
	3	50	3,543	50	3,090	0	−453
2. M	4	53	2,758	42	2,687	−11	−71
	5	47	2,958	49	2,555	+2	−403
	6	51	3,765	49	3,226	−2	−539
	Mean	49	3,325	50	2,986	+0.3	−338 (10.2%)
		Control		Ethylvinyl Ether		Difference	
1. F	1	50	3,473	58	2,777	+8	−696
	2	44	3,299	77	2,674	+33	−625
	3	46	3,853	92	3,127	+46	−726
2. M	4	58	3,293	76	3,027	+18	−266
	5	54	3,697	65	3,294	+11	−403
	6	53	3,561	74	2,823	+21	−738
	Mean	51	3,530	74	2,954	+23	−575 (16.3%)

SUMMARY

These experiments show that in mice trifluoroethylvinyl ether is more potent than its non-fluorinated analogue ethylvinyl ether. The ratios, AD_{50}/LD_{50}, for the two agents are statistically the same.

The anesthetic indexes of trifluoroethylvinyl ether and ethylvinyl ether measured on the Rhesus macacus monkey are statistically the same. However, in the monkey, as in the mouse, trifluoroethylvinyl ether appears to be the more potent of the two agents.

Trifluoroethylvinyl ether shares with diethyl ether a curarimimetic action of about the same degree of intensity. Under ethylvinyl ether anesthesia this curarimimetic action prevails to a limited degree.

Under deep anesthesia in the monkey with either trifluoroethylvinyl ether or ethylvinyl ether there is a slight degree of depression in oxygen uptake. There is no statistical difference between this effect of the two agents. Diethyl ether elicits a depression of oxygen uptake of the same order of magnitude.

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