ANESTHESIA XLVI. FLUORINATED ETHYLENES AND CARDIAC ARRHYTHMIAS INDUCED BY EPINEPHRINE[1]

RAYMOND M. BURGISON, W. EDWARD O'MALLEY, CLAIRE K. HEISSE, JANE W. FORREST AND JOHN C. KRANTZ, JR.

Department of Pharmacology, University of Maryland School of Medicine, Baltimore, Maryland

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In former studies (1948, 1949) the authors showed that ethylene appeared to be unique among the gaseous and liquid hydrocarbons in that upon inhalation it did not sensitize the myocardium to epinephrine. This same property was shown to prevail with the deuterocarbon analogue of ethylene (1951). Recently our studies with fluorinated hydrocarbons and ethers led us to the observation that perfluoro ethyl ether was devoid of anesthetic properties (1953). Indeed it appears that in ethers and hydrocarbons the anesthetic potency bears an inverse ratio to the degree of fluorination. It occurred to us that it would be of interest to investigate the effect of fluorination in the aliphatic hydrocarbons upon cardiac automaticity.

EXPERIMENTAL PROCEDURE. Electrocardiograms, lead II, were recorded from the unanesthetized animals. Epinephrine hydrochloride solution, 1,100,000 (preserved with sodium bisulfite), 0.01 mgm./kgm., was injected intravenously. The injection was made during a period of 25 to 40 seconds. At the end of the injection (usually the beginning of the effect) another tracing was made. Subsequently each animal was permitted to breathe a mixture of the compound in varying concentrations mixed with oxygen. Concentrations from 25 to 50 per cent were used. The closed circuit procedure was employed. When the inhalation had continued for 5 to 15 minutes the foregoing experimental procedures were again carried out.

RESULTS. The results of these studies with various halogenated hydrocarbons are shown in table 1.

One of the dogs which was used for the difluoroethylene experiment was permitted later to inhale monochloro-difluoroethylene. The injection of epinephrine in each experiment produced strikingly dissimilar effects upon the myocardium, as shown in figure 1.

The data in table 1 show that the fluorination of ethylene does not alter its property of being incapable of sensitizing the heart to epinephrine. Chlorination of ethylene, however, produces compounds which cause sensitization and multifocal ectopic ventricular beats. Partial fluorination of chlorinated ethylene likewise produces compounds capable of sensitization of the myocardium.

Of the nine halogenated ethylenes tested only those containing chlorine in the molecule were found to elicit anesthetic effects. These facts are in accord with

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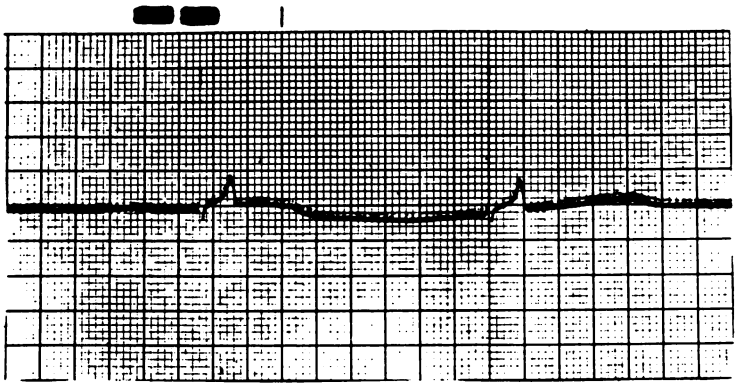
TABLE 1

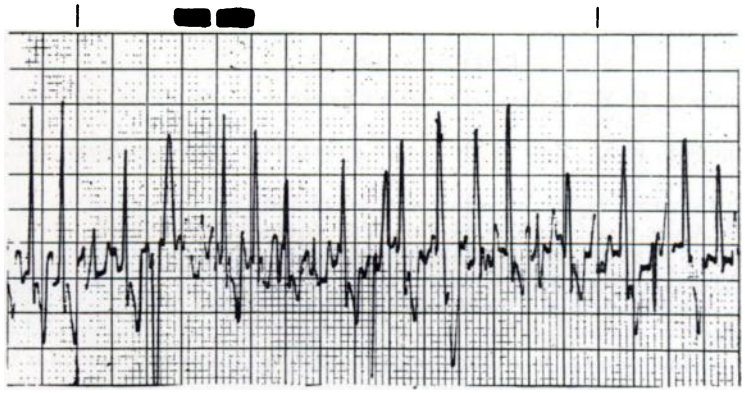
Summary of myocardial sensitization

Name of Compound	Number of Animals* in Which Sensitization of Myocardium Occurred and Number Used
Tetrafluoroethylene	0/4
Tetrafluoroethylene (cats)	0/2
Difluoroethylene	0/8
Difluoroethylene (cats)	0/2
Trifluorochlor-ethylene (Genetron-265)	4/4
Monochloro-difluoroethylene	4/4
Trichloro-monofluoroethylene	2/2
Cis-dichloroethylene	4/4
Trans-dichloroethylene	5/5

* Dogs unless otherwise stated.



DIFLUOROETHYLENE
and EPINEPHRINE



MONOCHLORO - DIFLUOROETHYLENE
and EPINEPHRINE

FIG. 1

the findings of Robbins (1946). He observed that the introduction of another halogen atom into a fluorinated hydrocarbon increased greatly the anesthetic potency of the latter. It is of interest that Virtue and Weaver (1952) observed that sulfur hexafluoride elicited mild anesthetic effects in man.

Garb and Chenoweth (1948) suggested the hypothesis that different concentrations of the hydrocarbon reduce myocardial irritability in various portions of the ventricles. This gives rise to small temporary blocks in the presence of epinephrine and certain other sympathomimetic amines. For some reason inexplicable to us, ethylene is incapable of producing these changes in cardiac rhythm. The fluorine-carbon bond is a strong form of chemical linkage and perfluoroalkanes are noted for their extreme stability and unreactivity. On the other hand, the fluorinated olefins display marked chemical activity in their ease of oxidation and polymerization, and the readiness with which they enter into addition reactions. Fluorine with an atomic number of 9 fits close to the carbon nucleus and resembles closer a carbon-hydrogen bond than does a chlorine-carbon bond. Chlorine has an atomic number of 17 and is much more easily removed from its carbon linkage than is fluorine. It is possible that this phenomenon is associated with the molecular volume and volatility of the agents. This in turn likely determines their ease of passing through cellular membranes. Ethylene is a very flat, two-dimensional type of molecule with a very small molecular volume. This property is shared by the fluoroethylenes but not chloroethylene or propylene. Indeed ethane and methane, which produce sensitization, are more three dimensional than is ethylene. The entire phenomenon remains puzzling and presents interesting challenges for further study.[2]

CONCLUSION

Tetrafluoroethylene and difluoroethylene, like ethylene, are incapable of sensitizing the myocardium upon the injection of a challenging dose of epinephrine.

The chlorination of difluoroethylene produces a mixed halogenated ethylene which causes cardiac sensitization.

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