Clinical Anesthesia

Halogenated Anesthetics

Joseph F. Artusio, Jr., M.D./Editor-in-Chief

1/1963

Halogenated Anesthetics

Joseph F. Artusio, Jr./Editor

BLACKWELL SCIENTIFIC PUBLICATIONS
OXFORD

Printed in the United States of America
Library of Congress Catalog Card Number 62-21099

The Introduction of a New Series of Monographs

The planning and the eventual introduction of a new series of monographs in the specialty of anesthesiology have proved to be a stimulating undertaking. It has been a satisfaction to watch the series develop from a simple idea, and to observe its gradual maturation in purpose, content and style.

The early months of preparation were concerned with the establishment of an over-all policy for these new monographs, and with the selection of a group of able Editors who would express the consensus on clinical management during anesthesia, and care during the postanesthetic period.

The Editors have been chosen carefully, and, as you review their names and their positions in Anesthesia in this country, you will see that both excellence and national representation were sought. According to present plans, each one of these Editors will assume responsibility of publishing one volume every five years. This will not be too burdensome for any one Editor, and will give each Editor ample time to plan his issue, choose his contributors, and present the material in the best style of current medical writing.

Subscribers to this series of monographs may wonder how this particular publication fits into the literature of anesthesiology, and why it was felt that this type of publication was needed in the specialty. The existing journals in anesthesiology are excellent. However, they are interested primarily in publishing either material of a research nature, or presentations which are primarily clinical case reports. The purpose of this series of monographs, however, differs from that of existing journals of anesthesiology. In the first place, the monographs will be intensely clinical. Each

issue will be devoted primarily to the presentation of a complete clinical subject from the standpoint of anesthetic management, or to a discussion of the clinical use of groups of anesthetic agents and their application to various clinical situations. Historical and research aspects of each subject will be held to a minimum, and used only to substantiate the clinical recommendation of patient management. At present there is not a single place in our anesthesia literature where one can find a consensus of opinion concerning anesthesia management in all facets of a subject. In order to obtain this type of information the anesthetist has to find specific articles in many journals, and bring the data together for himself.

In the series it is the aim to make the subjects timely, varied and interesting. Each Editor of an issue will procure, to the best of his knowledge, the most able men in this country and abroad to present a particular facet of a clinical subject.

As each number is published, the Editor-in-Chief and each Editor will welcome comments concerning the material that is covered and the style of presentation. They will also welcome suggestions as to subjects to be discussed in future issues.

I hope that you enjoy this series, and that it does not became a piece of unnecessary literature which so often clutters our medical information. I also hope that the monographs will be of value to you and your students, and that they will be, as long as the material remains current, a source of ready reference in your library.

JOSEPH F. ARTUSIO, JR., M.D.
Editor-in-Chief

Contributors

Joseph F. Artusio, Jr., M.D.
Professor of Anesthesiology in Surgery, Cornell University Medical Center, New York, N. Y.

Peter H. Byles, M.B.
Assistant Professor of Anesthesiology, State University of New York—Upstate Medical Center, Syracuse, N. Y.

Allen B. Dobkin, M.D.
Professor and Chairman, Department of Anesthesiology, State University of New York—Upstate Medical Center, Syracuse, N. Y.

William H. L. Dornette, M.D.
Professor of Anesthesiology, University of Tennessee College of Medicine, Memphis, Tennessee

Contents

CHAPTER 1. General Considerations of Halogenated Anesthetics 1
by Joseph F. Artusio, Jr., M.D

CHAPTER 2. Chloroform 23
by Lucien E. Morris, M.D.

CHAPTER 3. Trichlorethylene Anesthesia 43
by Allen B. Dobkin, M.D., and Peter H. Byles, M.B.

CHAPTER 4. Clinical Anesthesia with Fluroxene 67
by William H. L. Dornette, M.D.

B. E. Marbury, M.D.
Clinical Associate Professor of Anesthesiology in Surgery, Cornell University Medical Center, New York, N. Y.

Lucien E. Morris, M.D.
Clinical Professor of Anesthesiology, University of Washington; Director, Anesthesia Research Laboratories, Providence Hospital, Seattle, Washington

Robert I. Schrier, M.D.
Assistant Professor of Anesthesiology in Surgery, Cornell University Medical Center, New York, N. Y.

C. R. Stephen, M.D.
Professor of Anesthesiology, Duke University Medical Center, Durham, North Carolina

Alan Van Poznak, M.D.
Clinical Assistant Professor of Anesthesiology in Surgery, Cornell University Medical Center; Assistant Attending Anesthesiologist, The New York Hospital-Cornell Medical Center, New York, N. Y.

CHAPTER 5. Clinical Use of Halothane 81
by C. R. Stephen, M.D.

CHAPTER 6. Clinical Administration of Methoxyflurane 103
by Alan Van Poznak, M.D.

CHAPTER 7. Tribromethanol (Avertin) 121
by Robert I. Schrier, M.D.

CHAPTER 8. Ethyl Chloride 131
by B. E. Marbury, M.D.

INDEX 139

Chapter 1

General Considerations of Halogenated Anesthetics

Joseph F. Artusio, Jr., M.D.

HISTORY OF HALOGENATED HYDROCARBONS

Halogenated compounds have been used as anesthetic agents almost from the beginning of the era of general inhalation anesthesia. In 1847 Sir J. Y. Simpson[13] introduced chloroform as a clinical anesthetic, and halogenated hydrocarbons were destined from this date to play an important role in clinical anesthesia. Many years elapsed before Heyfelder introduced ethyl chloride in 1848 as a general inhalation anesthetic for man. Almost 40 years elapsed until 1926 when tribromethanol mixed with amylene hydrate and called Avertin fluid[2] was introduced. This resulted in two clinically useful halogenated hydrocarbons and one useful brominated alcohol. However, liver toxicity from the use of chloroform, cardiac irregularities associated with the administration of ethyl chloride, and prolonged sleeping time and depression of respiration and circulation due to Avertin fluid have caused these three halogenated compounds to almost disappear from the armamentarium of the anesthesiologist of today.

Interest in this group of compounds was renewed in the 1940's by the studies of the late Dr. Benjamin Robbins[12] and in the 1950's by the work of Raventos[11] and Suckling[14] in England, and of Krantz and associates,[7] Van Poznak and Artusio,[15, 16] Chenoweth and co-workers,[3] and Fabian and his colleagues in this country. From the work of these men have come interesting new halogenated compounds which have become clinically useful anesthetic agents — halothane, which has gained great popularity, fluroxene, in which renewed interest is being shown, and methoxyflurane, the newest of the three

A CHRONOLOGY OF EVENTS IN THE DEVELOPMENT AND APPLICATION OF THE HALOGENATED AGENTS*

1648 / Glauber discovered ethyl chloride.

1771 / Scheele discovered fluorine.

1774 / Scheele discovered chlorine.

1831 / Guthrie, Liebig, and Soubeiran independently discovered chloroform.

1847 / Flourens discovered anesthetic properties of ethyl chloride and chloroform.
Simpson used chloroform clinically.

1864 / Fisher discovered trichlorethylene.

1880 / Heyfelder used ethyl chloride for general anesthesia.

1934 / Jackson used trichlorethylene clinically.

1951 / Shukys synthesized fluroxene.

*Taken from *LANDMARKS IN THE DEVELOPMENT OF ANESTHESIOLOGY*, published by the Ohio Chemical and Surgical Equipment Company.*

1953 / Krantz discovered anesthetic properties of fluroxene.
Sadove used fluroxene clinically.

1956 / Suckling synthesized halothane.
Raventos discovered anesthetic properties of halothane.
Johnson used halothane clinically.

1957 / Larsen synthesized teflurane.
Chenoweth discovered anesthetic properties of teflurane.

1958 / Larsen synthesized methoxyflurane.
Larsen, Chenoweth, and Shea discovered anesthetic properties of methoxyflurane.

1959 / Artusio and Van Poznak used methoxyflurane clinically.
Dishart synthesized halopropane.
Fabian discovered anesthetic properties of halopropane and used it clinically.

1960 / Artusio and Van Poznak used teflurane clinically.

It must be realized that these are but prototypes of new anesthetic agents to follow. Many of the halogenated anesthetics which are described in this particular monograph may no longer have a place in our armamentarium within a 10 year period. They may be replaced by other compounds in the halogenated series, or by an entirely different class of drugs still to be developed, which may prove to be better anesthetic agents, easier to administer, and less toxic to all organ systems.

ADVANTAGES OF NONFLAMMABLE AGENTS

There is considerable concern today relating to the problem of anesthetic explosions in operating rooms. Nonflammability has become an important prerequisite for new anesthetic agents and it would be extremely difficult for a new anesthetic agent, regardless of its excellence, to ever gain widespread use if it were flammable. Although very few anesthetic explosions occur throughout the world, each one is indeed a catastrophe.

The cost of the explosion proofing of operating rooms and refurbishing in existing structures is expensive. Although the cost is not prohibitively high in new construction, it is an additional cost which could be eliminated if all anesthetics were nonflammable. There is no doubt that in time of war or civilian disaster the nonflammable agents are much easier and safer to handle than are the flammable drugs. The danger from fire or explosion is always present when volatile, flammable liquids are transported. This could be entirely eliminated if all anesthetic drugs were nonflammable.

It is my belief, therefore, that research of the future should be confined to the nonflammable drugs, and that all efforts should be made to develop excellent anesthetic compounds which will neither explode nor burn in the presence of air or oxygen.

REQUIREMENTS OF A NEW ANESTHETIC AGENT

It may be asked how one proceeds to build a new anesthetic agent in this series of compounds, what physical and chemical properties should be sought for in relation to the molecular structure of a drug?

Physical State

At the outset, a decision must be made whether the physical state of the anesthetic be a gas or a volatile liquid at room temperature. Many points can be made for or against a particular physical state of an agent. A gas is more accurately metered than is a volatile vapor, but modern anesthetic liquid vaporizers deliver concentrations of an agent which can be controlled within limits. Transportation of gases in tanks is more difficult than transportation of bottles of volatile liquids and may be an important consideration for the development of liquid agents. If I had my unimpeded choice, I would choose to develop a drug that was a gas at room temperature and pressure, but it is simply a matter of personal preference, and should not constitute great concern to the individual who is planning a new drug.

Central Nervous System Depressant Properties

From the investigations of Dr. Van Poznak and myself,[15] a compound of the hydrocarbon series, other than a single carbon compound, must have some hydrogen present in the molecule to have sufficiently depressing properties on the central nervous system to make it a useful clinical anesthetic agent. I took exception to single carbon compounds, for this may not be true in the methane series of drugs. Throughout the range of halogenated hydrocarbons and ethers, individual agents will show mixed excitation and depression, and by the regulation of the amount of hydrogen, and the quantity and quality of halogen, basic carbon chain drugs can be produced

DICHLORODIFLUOROMETHANE

CCl_2F_2

ANIMAL	DOSE	ANESTHESIA	EEG	EKG	REMARKS
3 Dogs	50 %	Unsatisfactory	Grand Mal	St↓	Convulsions. Satisfactory anesthesia if combined with Thiopental or Succinylcholine.
2 Dogs	15 %	"	"	"	Convulsions.

Figure 1. Example of a perhalogenated methane which produces convulsion in the dog.

TETRAFLUORODICHLOROETHANE

$CF_2Cl\,CF_2Cl$

ANIMAL	DOSE	ANESTHESIA	EEG	EKG	REMARKS
1 Dog	50 %	Unsatisfactory	Grand Mal	Obscured Tachycardia	Severe convulsions. limiting respiration. Rapid recovery. No ill effects noted.
1 Dog	25 %	"	"	"	"

Figure 2. Example of a perhalogenated ethane which produces convulsion in the dog.

which have more depressing properties or more central nervous system exciting properties, so much so that some compounds produce so much excitation that any of their depressant properties are completely masked.

Potency

Upon the discovery of a compound that appears to have good central nervous system depressant properties in the experimental animal, it is then important to determine what percentage of the agent in oxygen is required to produce anesthesia. Potency should be considered under two general classifications: first, the absolute potency of a drug, and second, the drug's biologic potency. Absolute potency is by definition a concentration of the drug which produces the desired clinical effect, and, when exceeded, produces no greater effect as long as the subject is receiving adequate tissue oxygenation for metabolic processes. Biologic potency of an anesthetic refers to the ability of the drug to produce varying degrees of depression of the organism. A drug of high biologic potency would be one which would produce complete depression of the organism to eventual paralysis of the most resistant cells of the central nervous system which control respiration and circulation. Continued administration of full concentrations of an anesthetic agent of 100 per cent biologic potency produces death.

It seemed ideal to Dr. Van Poznak and myself, in the early phases of our conceptual thinking, that a new halogenated anesthetic should be a drug of limited biologic potency and have a specific absolute potency.[1] Our ideal goal still eludes us, that is, to produce a drug whose physical state, at room temperature and pressure, would be a gas, and which would only produce light to moderate surgical anesthesia at concentrations of no greater than 40 volumes percent of anesthetic agent in the inspired mixture with oxygen. There would remain 60 volumes per cent of oxgen in the inspired atmosphere to maintain adequate tissue oxygenation. This oxygen concentration would be three times ambient, resulting in a high partial pressure

of oxygen in the inspired mixture, which would tend to prevent hypoxia even during states of relative hypoventilation. The resultant compound would be intermediate between the weak anesthetic agents, nitrous oxide and ethylene, and the potent drugs like chloroform and diethyl ether.

The concept of a limited biologic potency is based on the premise that the biologic limit would prevent anesthetic overdose. Inadvertent death of the organism by the administration of too high concentrations of the anesthetic, or the accumulation in the tissues of a large quantity of the agent to the point of tissue toxicity, resulting from assisted or controlled ventilation would be prevented. The ideal anesthetic agent would have these limiting factors as an inherent property of the molecule itself, eliminating the danger of anesthetic overdose.

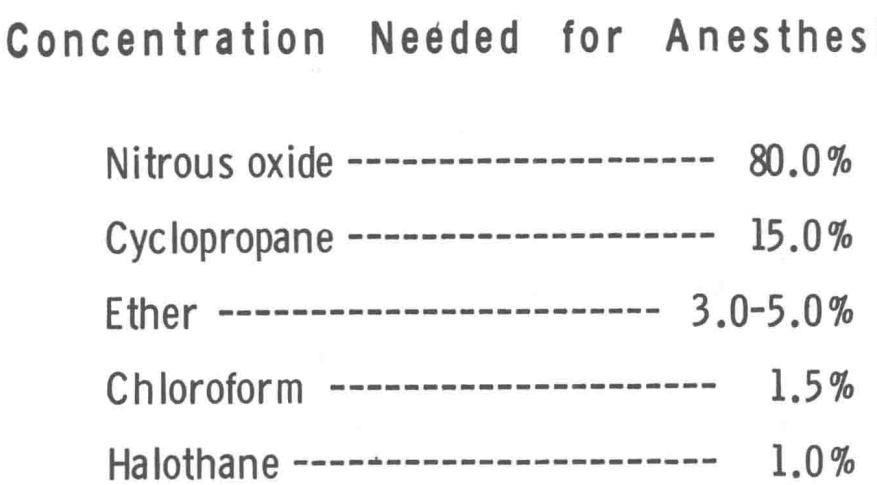

Figure 3. The range of inspired concentrations of several anesthetic agents necessary to produce light surgical anesthesia.

At present, our investigations have not developed the ideal and so-called "safe anesthetic" agent which meets the criteria of our concept of intermediate potency. However, anesthetic safety can be related to the saturated vapor pressure of a liquid agent, as there is an inverse relationship between saturated vapor pressure and boiling point, and the boiling point of a compound and its anesthetic potency vary in direct proportion. For these reasons it seemed logical to investigate compounds with higher boiling points and low saturated vapor pressures which could combine the properties of anesthetic potency and safety. The anesthetic safety factor of compounds with low saturated vapor pressures is associated with the few molecules of the anesthetic vapor on the surface of the liquid at any one time. With the few number of molecules of the vapor available it is almost impossible to introduce a sufficient quantity of agent into the inspired

mixture during the initial phase of anesthesia. Anesthetic agents with high saturated vapor pressures have large numbers of molecules of vapor over the surface of the liquid which makes possible sudden anesthetic overdose, either by deep inhalation or by assisted or controlled ventilation. The low saturated vapor pressure of methoxyflurane offers this advantage over the volatile liquids of high saturated vapors that are popular anesthetics today. It is true that the agents with low saturated vapor pressure decrease the speed of anesthetic induction when used as the sole anesthetic agent. However, the disadvantages of a decrease in induction time are far outweighed by the elimination of the danger of rapid initial anesthetic overdose.

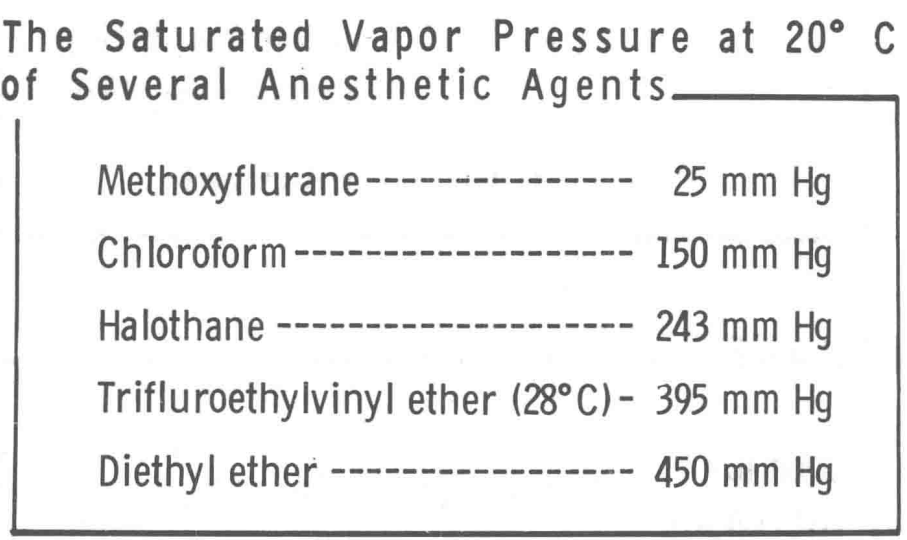

Figure 4. Saturated vapor pressures at 20° C of several commonly used anesthetic agents.

HALOGENATED HYDROCARBONS IN INVESTIGATION OF A NEW AGENT

The logical question arises in one's mind as to why so much investigation is being directed at halogenated hydrocarbons in search of a better anesthetic agent. We believe this to be due to the fact that various halogens can confer several desirable features for anesthetic agents.

Chlorine and bromine are able to confer various degrees of biologic potency on hydrocarbons or ethers, and the anesthetic potency of the drugs can, within limits, be adjusted readily by the choice of the number and position of chlorines and bromines on the basic molecular structure.

Hydrocarbons and ether, for the most part, are flammable in air or oxygen within certain limits because of the abundance of hydrogen in the

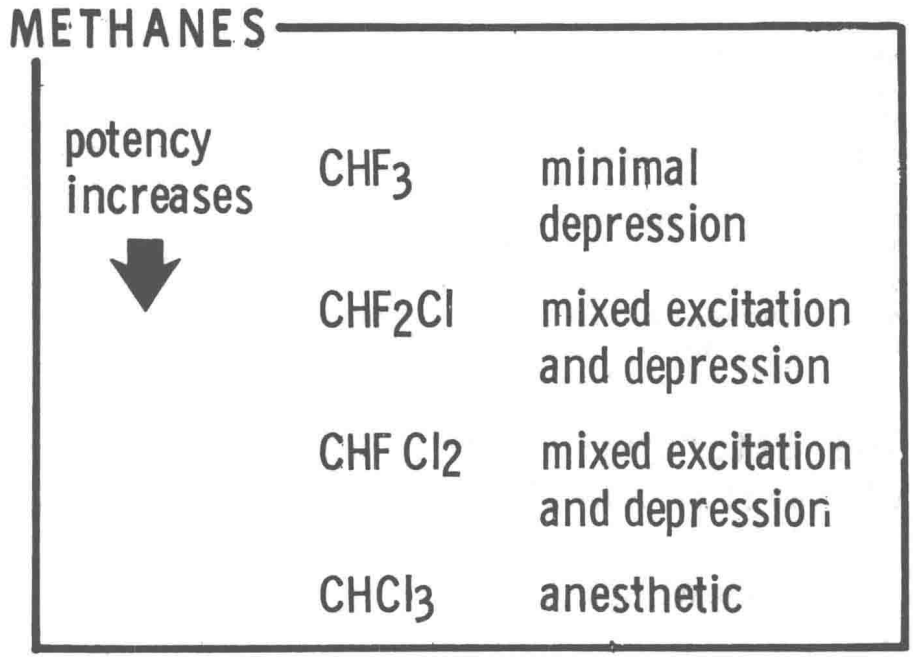

Figure 5. A series of halogenated hydrocarbons of the methane series listed in order of increasing anesthetic potency.

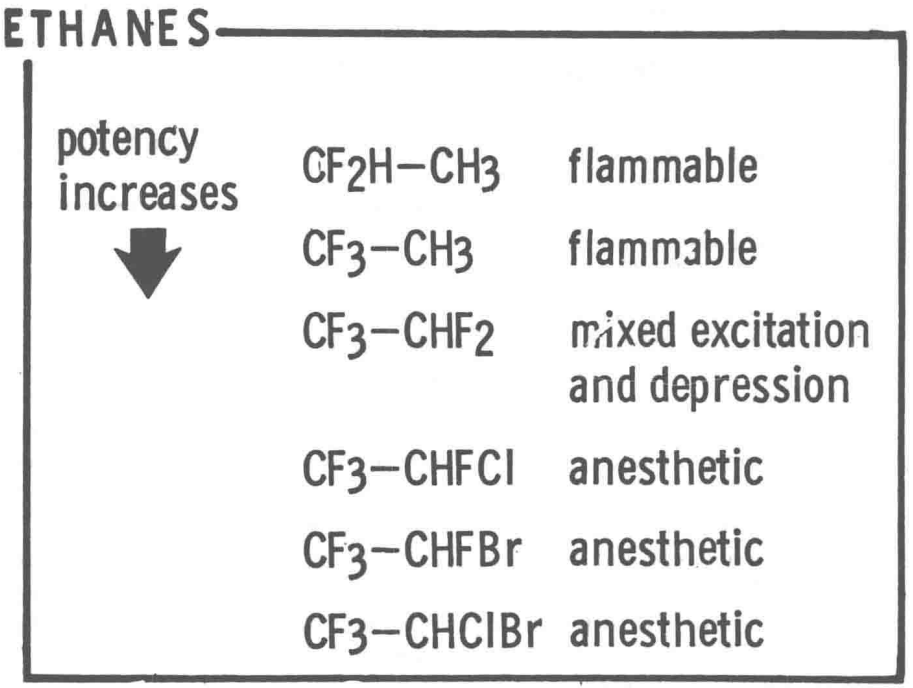

Figure 6. A series of halogenated hydrocarbons of the ethane series listed in order of increasing anesthetic potency.