International Journal of Drug Safety and Discovery

Loai Aljerf , Int J Drug Disc 2018, 2: 1
1: 010

Research

Halothane Anesthesia – Fact or Fallacy?

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Abstract

The goal of a clinical practice guideline is to distil a systematic review of evidence into recommendations intended to optimize patient care. Every year, a large number of Arcton bottles are produced. However, few studies have investigated the mechanism of the reaction of anesthetic general and anesthetic drugs, in humans and animals as mice. For instance, still no study can give an evidence of decreasing dose requirements of halothane during prolonged. Despite, some reports were interested in measuring the anesthetic potencies of nitrous oxide, isoflurane, enflurane, halothane, cyclopropane, and chloroform. The current paper aggregates different opinions about halothane anesthesia in clinical practice even few have considered the molecular basis for the immobilizing activity of anesthetics and we (the authors) are giving our scientific belief about anesthesia logic usage in relation to the chemical and physical behaviors of these compounds. This could lead to the improvement of safety and long-term outcomes of patients undergoing general anesthesia. By the end of this paper, we found that the unitary mechanism of anesthetic action cannot completely explain many phenomenal states as depression but can be supplemented with an intensive care in emergency.

Keywords: Halothane Anesthesia; Clinical Practice; Drugs; Cardiac Irregularities; Blood Pressure

Our assignment today is to talk about the way in which chemistry and physics can help in the choice of compounds to be tested pharmacologically as candidate anesthetics, and we shall illustrate this by reference to the work which led to the discovery of halothane (Fluothane). We suggest that of the properties which are wanted in an anesthetic there are three which can be fairly closely related to chemical and physical properties. These are (1) absence of chemical toxicity, (2) absence of inflammability and explosive hazards, and (3) anesthetic potency itself, and we shall show how one may attempt to design a molecule which will have these properties, and conclude with a general discussion of recent theories of relationships between molecular structure and anesthetic potency, with especial reference to the work of Liu et al. [1].

The first question we had to ask when, in 1951, scientists began thinking about searching for anesthetics was just what a good anesthetic ought to do. We consulted anesthetists in 2017 and were a little taken aback by the answer. A good anesthetic, we were told, should provide rapid and smooth induction not unpleasant to the patient with no irritation of the respiratory tract, good muscular relaxation, and rapid and easy control of the depth of anesthesia, a good margin of safety, absence of sweating and of secretion from the mucosa, no increase in capillary bleeding, no cardiac irregularities or adverse effects on any organs, compatibility with adequate oxygen, controllable blood pressure, good recovery with absence of vomiting and nausea, stability over soda lime, and that it should be noninflammable and nonexplosive—a formidable list.

Of course, we understand that some anesthetists prefer to have each physiological response under the control of a separate drug.

It might be thought that since the biological processes involved in anesthesia are so little understood, it would be impossible to rationalize the selection of compounds to test as anesthetics. This is not so. Of course, it is quite impossible to assess from chemical and physical properties whether a compound will be a practical anesthetic; far less could one hope to predict that a compound would be superior to those already in use. The verdict of the pharmacologist and of the anesthetist himself cannot be anticipated; but although one cannot predict how a compound will show up in the all important finer points of anesthesia, one may, by following the leads which are available, increase the chance of success by selecting the most profitable area of search.

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Sub Date: May 4th 2018, **Acc Date:** May 17th 2018, **Pub Date:** May 18th 2018.

Citation: Loai Aljerf and Nuha AlMasri (2018) Halothane Anesthesia – Fact or Fallacy?. Int J Drug Disc 2: 010.

Let us take first the question of toxicity. One way of reducing the risk that a compound will prove toxic is to work with compounds which are chemically inert and therefore unlikely to become involved in metabolic chemistry. One group of compounds which possesses a high degree of chemical stability is that of the fluorinated paraffins, in which chlorine and bromine may also be present.

Table 1 shows the formulae of some of these compounds which are widely used as refrigerants and in aerosols. They are known under the trade name, Arcton. The first two in the table, Arcton 4 and Arcton 6, are used as refrigerants. Arcton 6, Arcton 9, and Arcton 33 are used as propellants in aerosols. Paint, shaving soap, insecticide, and perfume are packed under pressure with these low boiling compounds. When pressure is released through a simple valve the mixture is ejected usually as a fine spray, the Arcton evaporates, leaving the other ingredient behind. Also in the table is the formula of halothane. In passing we might note that the second carbon atom of halothane has bonds with four different atoms and halothane should therefore exist in two optically active isomers. The commercial product should be the racemic mixture, but we do not know how to resolve it into the dextro- and laevorotatory forms.

Table 1: Some typical Arctons

CF_2HC1	Arcton 4
CF_2C1_2	Arcton 6
$CFHC1_2$	Arcton 7
$CFC1_3$	Arcton 9
$CF_2C1.CF_2C1$	Arcton 33
CF_3.CHBrCl	Halothane (Fluothane)

The Arcton compounds owe their use as refrigerants and in aerosols largely to their volatility, low toxicity and noninflammability properties which are desirable in an anesthetic inhalant. The first to suggest that the Arcton type of compound might be used as anesthetics appear to have been Barak et al. [2] who tested $CFHCl_2$ and CF_3HCl on mice. Both compounds produced convulsions. It is unfortunate that compounds of the Arcton type which are gases at room temperature frequently produce convulsions, as one might hope to find among these low boiling compounds, an anesthetic of sufficient power to permit its use with adequate oxygen but weak enough to serve some of the purposes to which nitrous oxide is put.

In 1994 Gryzagoridis and Findeis [3] tested forty-two compounds on mice and, with the more promising, on dogs. They recommended four compounds for further tests but no clinical trials ensued. Gryzagoridis and Findeis's results were of especial interest when examined in the light of Liu et al. [1] work, as will later be described. They did not, however, suggest any particular compound not tested by Liu et al. [1] as a potential practical anesthetic.

We might mention here that one difficulty in assessing the reliability of reported tests of compounds as anesthetics is doubt as to the degree of purity of the samples used, which is rarely indicated. One cannot be certain that when undesirable side effects are reported, they are due to the compound under test and not to some undetected impurity. But in the last few decades very searching analytical techniques have come into use, notably the gas chromatograph and the mass spectrometer, and we would not consider a compound as suitable for test as an anesthetic unless they were about 99.95 per cent pure.

Of course, application of these specialized techniques calls for the co-operation of specialists in analytical fields, and one cannot overstress the fact that the discovery and industrial development of even so simple a compound as halothane calls for the co-operation of very many skilled workers, chemists, engineers, physicists—quite apart from the work that is necessary on the biological side. The development of halothane has been very much a team effort.

We had at laboratory considerable experience in the specialized techniques for manufacturing the Arcton type of compound and in our desire to make further practical use of the special properties of these substances we decided to search among them and other fluorine containing compounds for an anesthetic.

Now the chemical inertness of these compounds is a consequence of the strong chemical bond between carbon and fluorine as a result of which the fluorine atom is extremely unreactive. The inertness of fluorine is especially pronounced in compounds containing the groups CF_3 - or CF_2 = which are not only very stable themselves but also stabilize links between adjacent carbon atoms and halogen. Thus in halothane the CF_3 - group reduces the reactivity of the chlorine and bromine on the adjacent carbon atom. It seemed probable, therefore, that compounds containing the groups CF_3 - or CF_2 = would, because of their high chemical stability be unlikely to interfere chemically with body metabolism. They should therefore have low toxicity.

So we hoped to minimize chemical toxicity by synthesizing very stable molecules. There is, of course, the other type of toxicity which is produced, like general anesthesia, not by a chemical, but by a physical mechanism, when an excessive concentration of the compound in the body produces undesirable and sometimes irreversible toxic symptoms. The ratio of this toxic concentration to that concentration which produces satisfactory anesthesia, which we believe you call margin of safety or anesthetic index cannot be predicted. There is, however, evidence accumulating that, among compounds of the Arcton type, the margin of safety may be greater in polar compounds or in compounds containing hydrogen. By "polar compound" we mean a compound in which the distribution of electrons is asymmetrical, so that all parts of the molecule have not the same electrical charge. The possibility of electrostatic interaction with other molecules is then present.

We concentrated in the first place on compounds containing the groups CF_3 - or CF_2= to obtain stability and, we hoped, absence of chemical toxicity. As for making compounds which were noninflammable and nonexplosive, we knew that if we kept the percentage of hydrogen in the molecule low, this requirement would be met.

We should perhaps interpolate here a remark about the photochemical stability of halothane. As you may know, unstabilized halothane evolves bromine when exposed for some days to bright light. This evolution of bromine is completely prevented by addition to Fluothane, before sale, of 0.01 per cent w/w of thymol. The thymol acts by mopping up the free radicals produced by light, which would otherwise lead to bromine evolution by a chain reaction. As an added precaution Fluothane is stored in brown bottles, but the thymol itself gives adequate protection.

The remaining problem was the choosing of compounds with adequate anesthetic potency. It might be thought that this would be a difficult matter, but, in fact, it is not, thanks principally to the work of Forman et al. [4], who was responsible for initiating the search which led to the discovery of halothane. In this, an earlier work [5] on the theory of narcosis proved of great value. We are using the term "narcosis" to denote the reversible inhibition of any biological function.

Liu et al's contribution to the theory of narcosis, and therefore of anesthesia, was to point out that the significance of data on narcosis is much greater when the concentrations of die drugs administered are expressed on a thermodynamic scale rather than in more usual ways, for example as percentages by volume.

Let us see how this works out. Table 2 shows results obtained by Eger [6] in experiments in which mice were anaesthetized by the compounds listed. The first column of figures gives the volume percentage of these compounds which were sufficient to produce anesthesia. You will observe that the figures vary from 0.5 to 100 per cent that is by a factor of 200.

In the second column of figures the concentrations producing anesthesia are expressed, as suggested by Liu et al. [1], as relative saturations, that is to say, as the ratio of the partial pressure producing anesthesia (p_a) to the saturated vapor pressure of the compound at the temperature of the experiment (p_z). This ratio, the relative saturation, when applied to water in the atmosphere gives the familiar relative humidity. You will notice that, when anesthetic concentrations are expressed in this way, the range of the values is greatly reduced. In this case it is 0.01 to 0.07, a factor of 7, compared with a factor of 200 when volume percentages are used.

The calculation of the ratio p_a/p_z should be clear from tables 3 and 4 which give results with die Arcton type of compound in anesthesia of mice. These tables include the saturated vapor pressure of the anesthetic at 20 °C and p_a (either determined experimentally or estimated from known vapor pressure curves of similar compounds) and the partial pressure for anesthesia p_z calculated from observed percentage by volume anesthetic concentrations. The pressure at which the experiment is conducted is assumed to be 760 mm Hg, so that the partial pressure for anesthesia equals anesthetic concentration per cent by volume x 760 / 100. Variations from 20°C and 760 mm Hg likely to occur during normal atmospheric conditions would not affect significantly the values for p_a/p_z which are given to one significant figure only.

The ratio p_a/p_z, the relative saturation for anesthesia, has a fundamental thermodynamic significance which we shall mention shortly, but first we shall give two more series of results in which anesthetic concentrations are again expressed as gaseous volume percentages and also as relative saturations.

Table 2: Anesthesia of mice

Substance	Anesthetic concentration per cent by volume	Relative saturation for anesthesia pa/pz
Nitrous oxide	100	0.01
Acetylene	65	0.01
Methyl ether	12	0.02
Methyl chloride	14	0.01
Ethylene oxide	5.8	0.02
Ethyl chloride	5.0	0.02
Ethyl ether	3.4	0.03
Methylal	2.8	0.03
Ethyl bromide	1.9	0.02
Dimethylacetal	1.9	0.05
Diethylformal	1.0	0.07
Dichloroethylene	0.95	0.02
Carbon disulphide	1.1	0.02
Chloroform	0.5	0.01
Data for Liu et al. [1] and Eger [6]		

Table 3 gives some results obtained by Zheng et al. [7]. The range of concentrations in volume percentage is 0.4 to 25 but in relative saturations 0.03 to 0.08. The results of Smith et al. [8], also with mice, are given in table 4. The figures for the last three compounds are of interest in that the relative saturations required to produce anesthesia are greater than with the other compounds in table 4 and the compounds in table 3. This may probably be attributed to the absence of hydrogen in the three compounds with the consequent effect on polarity or hydrogen bonding. It seems in fact that absence of hydrogen tends to reduce anesthetic potency—expressed on this relative saturation scale—but it has less effect on lethal concentration

Table 3: Anesthesia of mice

Substance	Boiling point	Vapor pressure at 20°C P_a mm Hg	Anesthetic concentration per cent by volume	Partial pressure producing anesthesia P_a mm Hg	Relative saturation for anesthesia P_a / P_z
$CF_2.CHBr_2$	73	104	0.4	3	0.03
$CF_2.CH_2Cl$	6	1400	8.0	60	0.04
$CF_3.CH_2Br$	26	600	2.8	21	0.04
$CF_2.CHCl_2$	29	550	2.7	21	0.04
$CFC1_2.CH_2$	32	470	2.5	19	0.04
$CHF_3.CH_2C1$	36	420	2.2	17	0.04
$CF_3Cl.CH_2Cl$	47	280	1.3	10	0.04
$CF_2.CH_2I$	55	200	1.3	10	0.05
$CHF_2.CH_2Br$	57	190	1.3	10	0.05
$CF_2Cl.CH_2Br$	68	130	0.8	6	0.05
$CF_2C1.CH_3$	-10	2300	25	190	0.08
Anesthetic concentrations by volume from Zheng et al. [7]					

Table 4: Anesthesia of mice

Substance	Boiling point	Vapor pressure at 20°C P_a mm Hg	Anesthetic concentration per cent by volume	Partial pressure producing anesthesia P_a mm Hg	Relative saturation for anesthesia P_a / P_z
$CF_2.CHBrCl$	50	243	0.9	7	0.03
$CF_2.CHBr_2$	73	104	0.6	5	0.05
$CF_2Cl.CHCl_2$	72	110	0.8	6	0.05
$CF_2.CHBr.CH_2$	49	260	2.2	17	0.07
$CF_2Br.\ CF_2Br$	46	290	4.1	31	0.11
$CF_2.CCl_3$	47	280	4.6	35	0.13
$CF_2Cl.CFCl_2$	48	270	5.6	43	0.16
Anesthetic concentrations by volume from Smith et al. [8]					

expressed on the same scale. The figures for lethal concentrations are not shown in the table. This suggests that, in the class of compounds which we have studied, those containing no hydrogen will have a smaller margin of safety and a lower potency compared with similar compounds containing hydrogen.

The results in tables 2 and 3 suggest the tentative hypothesis that any compound which is not chemically toxic will probably produce anesthesia, if administered at a relative saturation of 0.03 to 0.08. Such generalizations are, however, not strictly true [9] and we shall comment on some striking exceptions later. Nevertheless, this generalization holds as a rough rule for a surprisingly large number of compounds of relatively low molecular weight. The higher the boiling point of a compound the lower will be its saturated vapor pressure at any temperature. So we can get a good idea of how potent a compound will be as an anesthetic from its boiling point.

While on the subject of boiling point we might mention that we do bear in mind the fact that compounds boiling below about 30° C will have the practical disadvantage of necessitating storage in cylinders under pressure. On the other hand compounds with too high a boiling point may be excreted too slowly and delay recovery.

To return to the main theme, for one looking for an anesthetic, the principal advantage to be gained from Liu et al. [1]'s work is not that one can calculate in advance the approximate anesthetic potency of a compound, useful though this is. It is, we think, that Tanem et al. [10]'s treatment shows that a very large part of the difference between the anesthetic potencies of compounds when measured on the usual volume percentage scale is due to differences in saturated vapor pressure at the operative temperature. When these are allowed for, by expressing results as relative saturations, a much more uniform picture emerges, which shows, however, a previously unsuspected fine structure. Study of the residual differences which make up this fine structure can lead, in fact has led, to a much better understanding of the problem. Some otherwise obscure correlations are illuminated by Liu et al. [1]'s concepts. For example, it had been argued that the chlorine atom possessed some peculiar power of conferring anesthetic potency on a compound, and it had been suggested that this might be due to some special effect in the brain. But Gentili [11]'s work shows clearly that chloroform is a much more powerful anesthetic than methane because its vapor pressure (p_a) is always much lower than that of methane. Therefore, if anesthesia is produced by both at the same relative saturation (p_a /p_z) a much lower partial pressure (p_a) of chloroform will suffice to produce anesthesia than will be necessary with methane. Thus what was believed to be a peculiar property of the chlorine atom is brought into line with the behavior of any group or atom which, when substituted for hydrogen in a molecule tends to raise the boiling point. Sewell and Sear [12] have made a preliminary exploration of the relation of chemical constitution to narcotic potency measured on the thermodynamic scale. They said "We have now told you of some of the chemical and physical background which we had to help us when we started the work which led to the discovery of halothane". Some of the compounds which they chose to test were chosen because they were readily available but halothane, which was at the time an unknown compound, was selected on the basis of the considerations which they have outlined and specially made for testing as an anesthetic.

We should like in the short time that left us to bring up to date the discussion of the relationships between physical properties and anesthetic potency. First by saying a little more about relative works and then by alluding briefly recent theories advanced by Tung [13]. We have time for no more than a very quick and therefore imprecise exposition. Those who wish to know more of the subject will find the current paper well worth perusal.

Let us return first to the factor p_a/p_z, which has a more fundamental significance than we have so far explained. The factor p_a/p_z is approximately equal to the thermodynamic function known as "activity". Thermodynamic activities are always referred to an arbitrary standard state to which unit activity is assigned. In this paper the pure liquid is taken as the standard state with unit thermodynamic activity.

It is a fundamental property of thermodynamic activity of a substance, one expression of which is, as we have explained, p_a/p_z the relative saturation, that it is equal in all phases in equilibrium. By equilibrium is meant a steady state in which the rate of loss of anesthetic from the tissues is exactly balanced by the rate of uptake. It follows that, when an anesthetic has become distributed in equilibrium between the inspired air and the body tissues, its thermodynamic activity will be p_a /p_z in all the body tissues. This helps to circumvent the difficulty, which often arises in biological work, that one can discuss the concentration of a drug only as it is in the ambient medium, in the inspired air for example, when one is most interested in concentrations in the tissues.

There is a major group of compounds which diverge from Liu et al. [1]'s generalization in that they exhibit no anesthetic power and no toxicity at any thermodynamic activity. These are the perfluoro compounds such as perfluoropentane. Zheng et al. [7] found that the saturated vapor of pentane C_5H_{12} anaesthetized mice in 15 minutes, whereas the saturated vapor of C_5F_{12} perfluoropentane, had no effect whatever after one hour. Similar observations have been published by Shin et al. [14] and McLoughlin [15].

An explanation for these facts is offered by Woelfel et al. [16]. They correlate narcotic potency with the work required to replace a molecule in some biological tissue by a molecule of the narcotic. This work depends on the difference between the cohesive energy densities of the tissue and the narcotic. The cohesive energy density, as its name implies, is a measure of the forces holding a liquid together. Cohesive energy densities are dependent partly on molecular size which assumes great importance in Mullins's theories.

If two substances have very different cohesive energy densities, then much work will be required to replace a molecule of one by a molecule of the other. There will be a large heat of mixing. When an anesthetic and brain tissue form a solution which is far from ideal, the concentration of anesthetic in both air and brain which is necessary to produce anesthesia will be much higher than would be expected on the our basis.

Perfluorocarbons have very low cohesive energy densities compared with those of brain tissues, and even when the inspired air is saturated, enough perfluorocarbon to cause physiological activity is not transferred to the brain.

Carmona [17] suggests that the cohesive energy densities of the brain tissue affected by anesthesia are lower than that of body tissue in general. Therefore a good anesthetic should have a cohesive energy density such that it is more readily taken up by the brain than by other organs. In an anesthetic, like chloroform, which is liable to affect adversely some of the organs of the body, the cohesive energy density is too high and this permits it to be absorbed too readily in tissues other than the brain with consequent undesirable side effects. Klein et al. [18] suggested that since the low cohesive energy densities of fluorocarbons lead to physiological inactivity perhaps some fluorochloroparaffin (that is Arcton type of compound) might have a suitable cohesive energy density for anesthesia and still be stable and noninflammable. This suggestion was not made until after the discovery of halothane, although the last mentioned team did not aware of it.

We indicated earlier how the anesthetic potency of a molecule seems to be markedly affected by its polarity. It is unfortunately not possible at present to calculate the effect of polar interactions on cohesive energy densities. We cannot tell whether polarity will be shown, eventually, to be another factor operating by modifying thermodynamic properties and so fit into the general picture, or whether the wheel will make a full turn in that polar interactions, and perhaps hydrogen bonding, will be found to have a specific effect in the production of anesthesia.

You will have noticed that nothing has been said as to what is the mechanism by which anesthetics produce anesthesia. The theories which we have been discussing do not tell much about this, only that the mechanism must be thermodynamically reversible and physical. One may asks what of the future? The discovery of halothane has led to a revived interest in the Arcton type of compound: many more of them will, no doubt, be tested. Whether as a result, new compounds will find their way into clinical practice remains to be seen. We may, at least, confidently hope that the work will contribute to a better understanding of the mechanism of anesthesia.

Comparison of Seven Intravenous Anesthetic Agents in Men

Sir, —Drs. Holte et al. [19], reported a series of experiments on five volunteers with intravenous anesthesia state: "Because of its more detrimental effects, especially on respiration, hexobarbitone cannot be recommended". A great number of people would not agree with them on that point and it is noteworthy that Drs. Lerman and Jöhr [20], in the Pediatric Anesthesia, publishing the same experiments on the same volunteers enhanced by two more subjects state, "Hexobarbital: The mean period of apnea with this drug was 7 seconds with the mean dose of 517 mg/M^2. There was virtually no depression of the respiration or the metabolic rate"; and they go on to state, "on the whole hexobarbital had far less effect on either respiration or hemodynamic than thiopental and thiamylal for the corresponding state"; and later on, "all drugs significantly depressed oxygen consumption except hexobarbital"; and finally, "venous pressure was also reduced by all the drugs by at least 15 per cent with the least changes observed with hexobarbital and buthalitone". These latter findings are more in accord with other observations [21,22], and it would be interesting to know if hexobarbitone was the drug to which they were referring, and if it was, what the observations were on the last two subjects which so reversed their conclusions on the previous five.

Disclosure

No external funds and no funders have any role in the study design, in the collection, analysis and interpretation of data, in writing of the report, and in the decision to submit the article for publication. In addition, this research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Competing Interests

The authors declare that they have no competing interests.

Acknowledgement

Many thanks for St. Dr. Rawan AlHalak for her valuable collaboration in raising the quality of the pharmacological quality of this paper.

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