FLUOTHANE-ETHER: AN AZEOTROPIC MIXTURE[1]

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FLUOTHANE,[5] a volatile anaesthetic agent, is 1,1,1-tri-fluoro-2,2-bromochloroethane. It is non-inflammable and non-explosive (1). For the maintenance of anaesthesia, a concentration of 0.5 to 1.5 per cent is sufficient (2).

Induction is easy, rapid, with absence of coughing, vomiting, and salivary and bronchial secretions; surgical anaesthesia is present within 3 to 4 minutes. The changes in the level of anaesthesia occur rapidly so that a calibrated vaporizer is very useful to regulate the concentration. The recovery stage is calm and complete in 3 to 15 minutes following anaesthesia.

On the other hand Fluothane is only slightly analgesic before the loss of conjunctival reflex; it decreases the depth of respiration and depresses blood circulation (3). This results probably from a central depression and a decrease of the adrenalo-sympathetic response. Lastly, constant care is needed in Fluothane anaesthesia.

To provide an adequate oxygenation and a sufficient ventilation, oxygen should be given in excess, respiration should be assisted if necessary and only a vaporizer with accurate calibration should be used in order to prevent too deep a level of anaesthesia. If Fluothane anaesthesia is not well conducted, that is to say, if induction is too rapid and anaesthesia is too deep, a vagal hyperstimulation of the heart and a too rapid anaesthesia saturation of the cardiac muscle will lead to bradycardia which could result in cardiac arrest (3). Cardiac arrhythmias are not frequent; they seem to be related to a disturbance in the respiratory exchange, to Fluothane itself, and to the level of anaesthesia. These arrhythmias will decrease gradually with the experience and the skill of the anaesthetist. Following induction, a decrease of 20 to 50 mm. of mercury in the blood pressure is seen in most patients; later on, the blood pressure will vary with the neuro-vegetative status of the patient, with the lowering of blood volume, with the concentration of Fluothane in blood, with the position of the patient, the degree of hyperventilation and of positive pressure.

In securing Fluothane, an anaesthetic agent which offers such advantages as central sedation, potency, non-explosive atmosphere, and possibility of open-drop method, we searched for ways to raise its margin of safety.

The association of volatile anaesthetic agents is well known, and the idea of mixing di-ethyl ether with Fluothane has been put forward for the following reasons: generally, anaesthetic mixtures are made with agents of different boiling points and of varied pharmacological properties but of successive actions; quali-

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ties which often constitute a clinical disadvantage. However, in certain conditions, azeotropic mixtures result, that is, solutions with common boiling points, producing a concomitant but not successive action. In these circumstances, the proportions of the mixture remain constant. Yet, we have not heard of any azeotropic mixtures demonstrated in anaesthesia. In the hope that we might obtain a successful association and an azeotropic mixture, one part di-ethyl ether was mixed with two parts Fluothane for laboratory and clinical studies on August 27, 1957.

Our researches were carried out on toxicity, degree of inflammability, and on identification of an azeotropic mixture; the results obtained are reported in the complementary paper.

By a fortunate accident we were within 2 per cent of the azeotropic mixture likely to produce surgical anaesthesia with less than 1 per cent di-ethyl ether and 2 per cent Fluothane in the breathed gases. This azeotropic mixture boils at a constant boiling point and provides, in the vapour phase, a respirable gaseous anaesthetic mixture wherein the two components are present in essentially the same relative proportions as in the liquid which was volatilized.

The vapour of expiration was condensed by passing it through a trap cooled by means of a cooling mixture of acetone and dry ice; the composition of the condensate is identical with the liquid which was vaporized. This mixture is as stable on storage as Fluothane itself; it is non-inflammable in clinical use The lower limit of inflammability with oxygen is 10 9 per cent.

This discovery led us to investigate other mixtures, such as Chloroform-di-ethyl ether and Vinethene-di-ethyl ether, which, we found, give azeotropic compounds, but in proportions different from those already used in clinical anaesthesia.

The advantages of di-ethyl ether are well known (4). Di-ethyl ether decreases the intracardiac conductibility. If a displacement of the pacemaker is produced, it is not generally followed by extrasystoles; this can antagonize the increase of the myocardial excitability caused by Fluothane. At a low concentration, di-ethyl ether produces sympathetic stimulation that may partly counterbalance the hypotensive effect of Fluothane. By reflex action, di-ethyl ether increases the secretion of adrenalin and of noradrenalin.

Blood pressure, cardiac rhythm, and cardiac output show an initial elevation which augments to the point where 100 cc. of blood contain 91 to 110 mg. of di-ethyl ether (5). Cardiac output increases up to the second plane of the third stage. At this level, it is 241 per cent higher than normal (12).

At the second plane of the surgical stage, blood contains 120 mg. of di-ethyl ether in 100 cc. of arterial blood (5). Knowing that with a concentration of 25 mg. of di-ethyl ether in 100 cc. of arterial blood the respiratory volume augments, one can expect an improvement of the respiration (5). This concentration of di-ethyl ether is equal to that employed by Artusio to obtain analgesia is cardiac surgery, that is, 25 to 50 mg, of di-ethyl ether in 100 cc. of arterial blood (6). Thus mixed with Fluothane, di-ethyl ether may augment analgesia, increase ventilation, and diminish pain reflexes and reflex arrhythmia during a too superficial anaesthesia (Table I).

TABLE I

PERCENTAGE CONCENTRATION OF FLUOTHANE AND ETHER IN THE INSPIRED MIXTURE AND IN ARTERIAL BLOOD

Anaesthetic	Inspiration	Fluothane	Ether	Stage III Arterial blood (mg.) (hypothetical)
Fluothane	3%	3%	0%	15 mg.
Fluothane–ether	3%	2 04%	0 96%	Fluothane: 10 to 12 mg. Ether: 12 to 40 mg

The boiling point of Fluothane-ether is 51.5°C. compared with 50.2°C. for Fluothane and with 36.5°C. for di-ethyl ether; this makes the "Fluotec" vaporizer valuable in indicating the percentage of the mixture being delivered. The proportions of azeotropic mixture are 68.3 of Fluothane and 31.7 of di-ethyl ether for 100 cc. of the mixture (Table II).

TABLE II

BOILING POINTS OF FLUOTHANE, ETHER, AND THE AZEOTROPIC MIXTURE

Anaesthetics	Boiling point
Fluothane	50 2° C
Ether	36 5° C
Fluothane–ether 68 3 cc + 31 7 cc = 100 cc	51 5° C

With the "Fluotec" vaporizer, a surgical anaesthesia is obtained at the 2.5 to 3 per cent mark and maintenance is around 1.5 per cent, this gives in the inspired volume approximately 0.4 per cent to 0.95 per cent di-ethyl ether per volume and 0.8 per cent to 2 per cent Fluothane. It should be noted that 120 to 150 mg. of di-ethyl ether per 100 cc. of blood are obtained after inhalation of 2 to 4 per cent di-ethyl ether in the breathed air (5). A percentage of 0.4 to 0.95 di-ethyl ether per volume in inspired air could give, after several minutes, a concentration of 12 to 40 mg. in 100 cc. of arterial blood.

The lower limit of inflammability of di-ethyl ether with oxygen is 2.1 per cent this is a concentration much greater than the percentage of the mixture under study, if we consider that the vapour phase of inspiration and of expiration remains in the same proportion as the liquid composition.

Methods used included Boyle apparatus with or without "Fluotec" vaporizer, with open, semi-closed, or closed circuit; Heidbrink apparatus in semi-closed or closed circuit with oxygen; and open mask drop with continuous administration of oxygen by nasopharyngeal catheter.

Clinical Results

The mixture of Fluothane-ether gives an induction, an anaesthesia, and a recovery quite similar to those observed with Fluothane alone: rapid and easy induction without secretions and early depression of pharyngeal and laryngeal reflexes. Following induction with thiobarbiturates, the inhalation of the azeotropic mixture presents no difficulty, but one must correct by manual assistance the respiratory depression which prevails to a certain degree; however, ventilation is better than with Fluothane alone. Minute volume is increased by 20 per cent. Studies of the minute volume with Fink's valve and rotameter and with the "Ohio minute volume meter" show that, with Fluothane-ether, the minute volume increases during induction and also during maintenance under light anaesthesia; in the second plane with intubation and with absence of surgical stimulus, minute volume is augmented by one litre.

Hypotension is not constant; sometimes it will be 20 mm. of mercury or more during too rapid an induction, but, during maintenance, it tends to return to nearly a normal level. Nevertheless, especially in semi-closed and closed circuit, minute volume depression and apnoea happen quickly when Fluothane-ether concentration is increased and occur generally with a gradual fall of blood pressure. However, at this stage, peripheral circulation is better than with Fluothane alone. In some patients, it is not a fall of blood pressure but arrhythmia which accompanies the respiratory depression. When this happens, one must close the vaporizer and assist the respiration until a lighter plane of anaesthesia is obtained. Controlled respiration must always be done after having decreased the percentage of the mixture; that is to say, the potential hazards, although diminished, remain the same.

Eye signs are a reliable guide during induction and maintenance: pupils may dilate during the second stage and contract at the third stage to remain pin-point at the third plane. Eyes may open in deep anaesthesia.

The conduct of anaesthesia is easier and the margin of safety is greater. Most of our patients (Table III) were anaesthetized under closed circuit with pure oxygen. Flaxedil was used in small doses to obtain relaxation during maintenance, blood pressure and pulse rate increase with this drug.

Many patients have been anaesthetized several times with the mixture; they had no apprehension with the repeated inductions and no signs of intoxication postoperatively. In the series with Fluothane alone, three cardiac arrests supervened with complete recovery to normal (7, 8). In the series with Fluothane-ether, no cardiac arrest took place. With the visoscope, under Fluothane-ether anaesthesia and in comparison to Fluothane anaesthesia alone, the electrical modifications are not diminished in the initial phase of the ECG, but are considerably minimized in the intermediate and final phase of the ECG tracing.

The analysis of the liquid in the vaporizing bottle of the circuit showed no decomposition after several days of use. On one occasion, the water accumulated in one bottle for one month showed a small fraction of free acids, but this was insignificant in practice (analysis suggested and made by Dr. Carl Von Seemann)

TABLE III

SUMMARY OF CASES ANAESTHETIZED WITH FLUOTHANE AND WITH THE FLUOTHANE-ETHER MIXTURE

Surgical procedures with Fluothane without ether			3,016
Surgical procedures with Fluothane + ether			
Minor		1,323	
Major		1,121	
			2,444
Techniques			
Fluothane + ether	1,052		
Fluothane -- ether + Pentothal	687		
Fluothane -- ether + Neraval	705		
Intubation			
No intubation	804		
Intubation without relaxant	616		
Intubation with Anectine	740		
Intubation with Flaxedil	284		
TOTAL			5,460

Samples of the vaporized mixture taken with a syringe will not ignite if a lighted match is introduced into the syringe; these samples were taken from the anaesthetic bag, from the circuit tubes and from the endotracheal tube during expiration.

On three occasions, during an anaesthesia of four-hour duration conducted with a one-way vale, the vapours of the expiration were collected and condensed in a glass flask refrigerated with acetone and dry ice. The composition of the condensed liquid was identical with the liquid which was vaporized. This recovered Fluothane-ether and the water of expiration contained no free acid.

The mixture of one part of Fluothane with one part of di-ethyl ether was experimented with in the open drop method and with an anaesthetic machine; induction is easy but slower, respiration is further improved, and there is no hypotension.

To sum up, this clinical and experimental observation, based on a total of 5,460 cases (7–11) of which 2,444 are with Fluothane-ether, enables us to foresee a more extended use of the Fluothane-ether azeotropic mixture.

RÉSUMÉ

Le mélange deux parties de Fluothane pour une partie d'éther fut étudié au point de vue de solution, toxicité, inflammabilité, puissance et réaction.

Les analyses de laboratoire nous ont démontré que le liquide de composition est azéotrope dans le voisinage de ces concentrations, de même que dans la phase gazeuse et dans la partie récupérée de l'expiration.

Au point de vue chimique, il est non-toxique et reste stable pendant plusieurs mois.

La limite inférieure d'inflammabilité est de 10.9% dans l'oxygène.

Au point de vue clinique, la fraction éther semble jouer un rôle stimulant sur la respiration et la circulation et augmenter ainsi la marge de sécurité. Si l'on augmente la concentration d'éther, l'effet est encore plus marqué.

L'expérience de 2,444 anesthésies administrées avec ce mélange nous porte à croire que cette méthode peut être utilisée avec avantages.

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