PHYSIOLOGICAL MEASUREMENTS DURING ANAESTHESIA WITH FLUOROMAR

BY

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Trifluoro-ethyl-vinyl-ether (Fluoromar) has been reported (Orth, 1955) to be a non-irritating, rapid-acting anaesthetic agent. The lower flammability limit is 4 per cent in oxygen or air (ethyl ether, 2 per cent) and the minimum ignition energy is higher by many fold than that of diethyl ether or divinyl ether at the same concentrations (Moen, 1956). It is obviously desirable to minimize the explosive hazard in operating rooms, so it seemed worthwhile to investigate some of the variations in physiological functions that might occur during the use of Fluoromar as an anaesthetic agent.

METHODS

Preliminary observations were carried out using dogs as subjects. They were anaesthetized with Fluoromar either (a) with a mask directly, (b) after introduction of an endotracheal tube following administration of a paralytic dose of suxamethonium, or (c) after a small intravenous dose of thiopentone. The animals were allowed to awaken from the thiopentone anaesthesia and then anaesthetized with Fluoromar through the endotracheal tube. Adrenaline was given to 4 of these animals, both before and after anaesthetization with Fluoromar, according to the technique of Meek, Hathaway and Orth (1937).

Surgical patients were anaesthetized by three different techniques. (1) Open drop technique was used with infants and children. (2) Anaesthesia was induced in patients with thiopentone and maintained using a closed circle absorption system with Fluoromar as the anaesthetic agent throughout the rest of the procedures. (3) Twelve patients were studied using Fluoromar as the only anaesthetic agent. Control chemical analyses were required, so these patients were selected on the basis of their being in the hospital at least two days pre-operatively in order that bleeding (Duke, 1919) and coagulation (Lee and White, 1913) times, blood volumes (Crispell, Porter and Nieset, 1950; Storaasli, Kreiger, Friedell and Holden, 1950), blood glucose (Nelson, 1944) and blood urea (Karr, 1924), as well as bromsulphalein (BSP) retention tests (Rosenthal and White, 1925) and urea clearances (Karr, 1924; Folin and Youngberg, 1919; Youngberg, 1921) could be done before surgery. Blood glucose and blood urea were determined on a sample taken immediately before in-
duction. Anaesthesia was induced with Fluoromar and oxygen using a closed circle absorption system. Tracheal intubation was performed. No anaesthetic or relaxing agent other than Fluoromar was used. After one hour of anaesthesia, the bromsulphalein retention, blood volume, bleeding and coagulation time, blood glucose and blood urea values were again determined. Fluoromar was therefore given to the patient for somewhat more than 1.5 hours before the surgery was started. BSP retention was followed for several days or until it had returned to nearly control values. Urea clearance and blood glucose determinations were repeated the morning following surgery.

During these anaesthetic procedures the Monaghan ventilation meter was used to determine the effect of Fluoromar on tidal volume. Electroencephalographic tracings were made. The surgical procedures carried out using this technique included: 1 cholecystectomy; 1 laminectomy; 3 hysterectomies; 2 radical breast excisions; 1 breast biopsy; 1 excision of ovarian tumour; 1 pelvic node dissection; 1 femoral arterial graft; 1 gastrectomy. Electrocardiographic tracings were made at frequent intervals throughout 10 of these procedures.

RESULTS

The results may be divided into three parts; one includes the work with dogs; the second describes the measured values from the 12 patients in group 3; the third involves clinical observations.

I. Results Using Dogs.

Preliminary work with dogs indicated that Fluoromar was not especially irritating, that respiration was slightly if at all affected, and that salivation was minimal.

Control injections of adrenaline to 4 animals produced ventricular abnormalities as would have been expected. After the animals were asleep with Fluoromar, adrenaline injections were repeated with at least 15 minutes equilibration on Fluoromar and at least 30 minutes between injections of adrenaline. The records showed fewer irregularities when adrenaline was injected during the Fluoromar anaesthesia than during the control period. After waking, one of the animals was anaesthetized for 15 minutes with cyclopropane and then adrenaline injected a third time, allowing more than 30 minutes between adrenaline injections. This dog developed ventricular fibrillation (see chart 1).

II. Laboratory Determinations.

Table I* presents the analytical values obtained from the 12 patients in group 3. No significant changes in the values of the coagulation time, total blood volume, red cell or plasma volume, haematocrit or blood urea were found during the course of these observations. Bleeding time increased from an average 97 seconds to 123 seconds following one hour of anaesthesia with Fluoromar. These values had returned to

*See page 421.

CHART 1 (opposite)
7 kilogram dog.
A. Control awake, 10.55 a.m.
B. Adrenaline, awake, 11.00 a.m.
C. Asleep with Fluoromar, 12.06 p.m.
D. Adrenaline while asleep with Fluoromar, 12.08 p.m.
E. Asleep with cyclopropane, 12.35 p.m.
F. Adrenaline while asleep with cyclopropane, 12.42 p.m.
normal (94 seconds) the first postoperative day. Blood glucose values were significantly elevated from an average of 80 to 114 mg/ml during an hour of Fluoromar anaesthesia. BSP retention was elevated at the end of the hour of Fluoromar anaesthesia from 7 to 21 per cent. Following operation, these BSP values returned to normal as rapidly as would have been expected after the use of other anaesthetic agents (Waters, 1951). Urea clearance tests the day following surgery showed normal values. Numerical values for these tests are not given because some of the clearance values were maximum clearance and some were standard clearance, and not enough were done to treat them statistically. However, all were within normal limits.

III. Clinical.
Observations have been made on 100 patients. Fluoromar was not an irritating agent. The patients who received it were not excited by breathing this material. In fact, 3 of the 12 patients who were the subjects of group 3 requested specifically that they should not have an ether anaesthetic, but went to sleep with Fluoromar with no difficulty.

Patients lost consciousness rapidly when induced with Fluoromar. The induction, however, was not as rapid as it would have been with cyclopropane. They tolerated induction well with the Heidbrink absorber set at 6. There was no laryngospasm and no remarkable excitement period. Fluoromar seemed to prevent excessive “Bucking” on tracheal tubes. A few patients “bucked” when anaesthesia was quite light but, generally speaking, intubation was not stimulating to the patients. From 10 to 25 minutes were required before intubation could be carried out with Fluoromar as the sole agent administered. However, it was observed that when the patient’s jaw could be opened, the cords were abducted. Fluoromar caused no excessive salivation. Patients who had not received a belladonna drug had appreciable laryngeal secretions but seemed to salivate much less than would have been expected had ether been the anaesthetic agent. Ventilation by the patient was quite adequate so long as anaesthesia was light. Deeper planes of anaesthesia caused reduction in tidal volume. The physiological effects of Fluoromar differ from those of the commonly used anaesthetic agents, so the planes and stages of anaesthesia with Fluoromar have not been easy to determine by the usual criteria. Fluoromar had one respiratory effect similar to that of cyclopropane in that following a few large forced breaths, apnoea easily ensued. Assisted respiration very easily became controlled respiration.

Hypotension occurred in several patients without warning. It appeared before the usual signs of deep anaesthesia were noted and occasionally occurred while the patient was still moving. Electroencephalography with these patients produced the same types of tracings as have been observed with ether (Courtin, Bickford and Faulconer, 1950). They were not consistent with the usual clinical signs of depth of anaesthesia. Hypotension occurred without warning of change of state on the electroencephalogram. Reliance on e.e.g. patterns for
Fig. A
E.E.G. tracings
A—1. Awake. Systolic pressure 130 mm Hg.
A—2. Light anaesthesia. Systolic pressure 130 mm Hg.
A—3. Light anaesthesia, Systolic pressure 40 mm Hg.
A—4. Third plane anaesthesia. Blood pressure 50/20 mm Hg.
control of administration of Fluoromar seemed unjustified because severe hypotension frequently preceded any e.e.g. change. A few electroencephalographic patterns are presented. Figure A-1 is that of a patient awake whose systolic blood pressure was 130. Figure A-2 is the same patient in light clinical anaesthesia with blood pressure unchanged. Figure A-3 shows a record from the same patient who was still in light clinical anaesthesia but whose systolic blood pressure had dropped to 40 mm Hg due to the use of Fluoromar.

Figure A-4 shows the same patient in what was judged to be plane 2 of the third stage of anaesthesia clinically but whose blood pressure was 50/20 mm Hg. The low blood pressures in A-3 and A-4 followed immediately the use of high concentrations of Fluoromar. The pressures in both cases rose to normal within two minutes of eliminating Fluoromar from the breathing bag.

Figure B shows two records of a patient whose blood pressure dropped (due to Fluoromar) from 125 to 85 mm Hg. No clinical change was observed during this period. The e.e.g. voltage diminished moderately.

Figures C-1 and C-2 are e.e.g. records of a patient awake with a blood pressure of 114/75 mm Hg and asleep with a blood pressure of 89/50 mm Hg. When awake the tidal volume was 350 ml, when asleep the tidal volume was 450 ml. The second record was made when the patient was in light clinical anaesthesia.

Figure E is an e.e.g. made during Fluoromar anaesthesia which corresponds to the type that characterizes moderate surgical anaesthesia with ether. The blood pressure in this case was 90/70 mm Hg. The pre-induction blood pressure had been 110/70 mm Hg. Figure D is a record of a patient made when his blood pressure was 50 mm Hg systolic. This record is of the type corresponding to that showing deep anaesthesia when either cyclopropane or ether is used or a "danger" level with thiopentone. This patient was the only one of the series shown who was clinically deep in anaesthesia, that is, the pupils were dilating, fixed and dry; the tidal volume was only 50 ml and respiration was diaphragmatic in character. Pre-induction blood pressure was 100/60 mm Hg.

One striking feature observed during the use of Fluoromar was that when the blood pressure diminished, the pulse frequently slowed as well. The anaesthesia record (fig. F) is characteristic. No noticeable vasodilation occurred. Recovery has been rapid and without excitement.

Quite large quantities of this agent seemed necessary when using it by the open drop technique. By closed circle technique, the adult patients could be maintained in satisfactory surgical anaesthesia with approximately one ounce per hour of the material.

Some of the patients vomited. The list of operations indicates that surgery involved manipulation of the intestines so

**Chart 2 (opposite)**

M.B., Cholecystectomy, 56 years, female. E.C.G. tracings.

A. Control awake, 07.35 a.m., BP 120/80 mm Hg.
B. Asleep with Fluoromar, 07.52 a.m., BP 100/80 mm Hg. Note—Transient loss of P wave.
C. Asleep with Fluoromar, 08.33 a.m. BP 105/85 mm Hg. Note—Transient P wave change.
D. Asleep with Fluoromar, 10.00 a.m., BP 110/85 mm Hg. Typical throughout procedure except for the two brief periods illustrated in B and C.
E.E.G. Tracings. Note clinical change. Note blood pressure change.

C-1

C-2

E.E.G. Tracings.

C-1. Patient awake. Blood pressure 114/75 mm Hg. Tidal volume 350 ml.
C-2. Patient asleep. Blood pressure 80/50 mm Hg. Tidal volume 450 ml.

D

E.G.G. record. Plane 3, blood pressure 50 mm Hg systolic.

E

E.G.G. record. Plane 2, blood pressure 90/70 mm Hg.
the vomiting cannot be attributed to this agent. The general incidence of vomiting after the use of this agent has been low.

Chart 2 shows the only type of electrocardiographic abnormality observed with human beings asleep with Fluoromar in this study. It consisted of a wandering pacemaker (change in P wave), which is not considered to be significant.

**DISCUSSION**

The administration of adrenaline to animals anaesthetized with Fluoromar was followed by very little electrocardiographic change. In all 4 animals in which this was done, the tracing under those conditions showed much less abnormality than when adrenaline was administered to the animals when they were awake.
Fluoromar therefore showed a "protective" effect on the myocardium of these dogs. It seems particularly significant that on administration of adrenaline during Fluoromar anaesthesia one dog showed only an increase in cardiac rate with no change in the contour of the curve, while that same dog had ventricular fibrillation when adrenaline was injected during cyclopropane anaesthesia.

The BSP retention test showed no significant deleterious effects of Fluoromar anaesthesia on the liver. It is realized that this measures only one phase of liver function. Waters (1951) measured BSP retention in a series of patients who were receiving chloroform and another series receiving other agents as controls. He observed that 25 per cent of those anaesthetized with agents other than chloroform showed abnormal dye retention. He also observed that when retention occurred, it disappeared within a period of 7 to 10 days. Our series shows this same parallelism for the values had returned to approximately pre-operative values within 7 days.

As measured by urea clearance and blood urea values, no deleterious effect of Fluoromar on kidney function was observed.

Following ether or chloroform anaesthesia, blood sugar would be expected to rise 100 to 200 per cent (Adriani, 1952). The increase of 34 mg per cent of blood glucose in these patients is comparable to what one would expect using cyclopropane as the anaesthetic agent rather than either ether or chloroform.

The effect on respiration was minimal in light planes of anaesthesia. In deeper planes, respiratory volume diminished.

The effect on blood pressure seemed particularly significant. The mechanism of action is not known at this time so it cannot be stated whether use of Fluoromar is akin to controlled hypotension or not. Pressures returned to normal rapidly on discontinuance of the agent. Since cardiac output and tissue oxygenation in these circumstances are not known, no categorical statement can be made as to whether or not these hypotensive effects were good or bad. It would be desirable to determine cardiac output in these circumstances. Until more is known about the circulatory system during periods of hypotension it seemed unwise to rely on electroencephalographic patterns as a measure of depth of anaesthesia.

The lack of "bucking" with the use of Fluoromar seemed quite desirable. Certainly minute-to-minute control of the patient's condition is possible but it should be emphasized that such minute-to-minute or even second-to-second control is essential for its safe use. Inhalation of the material was pleasant for the patients.

The observations indicated that intubation can be done using Fluoromar alone but the time involved was such that routine use of this agent would probably be more efficient if the patient were induced with something like thiopentone and intubated using a relaxing agent before using Fluoromar alone.

The "wandering pacemaker" observed on the electrocardiographic tracing during Fluoromar anaesthesia has been observed with other inhalation agents (Kurtz, Bennett and Shapiro, 1936; Virtue and Pierce, 1951). Its exact significance has not been determined and certainly does
not point to a deleterious effect of Fluoromar on the myocardium.

**SUMMARY**

(1) Fluoromar is a nonirritating anaesthetic agent which produces little effect on respiration during early stages of anaesthesia.

(2) The common signs and stages of ether anaesthesia cannot be utilized for controlling administration of Fluoromar as an anaesthetic agent.

(3) Fluoromar frequently caused hypotension when no more than light planes of anaesthesia as judged by either e.g., tracings or the usual clinical signs of anaesthesia had been attained.

(4) Some increase in blood glucose, bleeding time and BSP retention was observed after one hour of Fluoromar anaesthesia.

(5) No significant change was observed in values of blood urea, total or fractional blood volumes, or coagulation time after one hour of Fluoromar anaesthesia.

(6) Kidney function was not measurably changed during one hour of Fluoromar anaesthesia.

**REFERENCES**


**Table I**

<table>
<thead>
<tr>
<th>Physiological variations following the use of Fluoromar.</th>
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<tbody>
<tr>
<td><strong>No.</strong></td>
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<td><strong>Avg.</strong></td>
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<td>Bleeding time (secs.)</td>
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<td>Coagulation time (minutes)</td>
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<td>Total blood volume (ml)</td>
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<td>Plasma volume (ml)</td>
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<td>R.B.C. volume (ml)</td>
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<td>Haematocrit (%)</td>
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<td>Blood glucose (mg%)</td>
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<td>Blood urea (mg%)</td>
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<td>B.S.P. Retention (%)</td>
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* B.S.P. values obtained 1 to 7 days later.