FLUOTHANE*: A NON-EXPLOSIVE VOLATILE ANAESTHETIC AGENT

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"Fluothane" is a new volatile anaesthetic agent developed and manufactured by Imperial Chemical Industries (Raventos, 1956; Raventos and Suckling, 1956). It is the most promising member of a series of agents with non-flammable and non-explosive properties which are being investigated independently by the Medical Research Council. It is a clear, colourless, heavy liquid with a specific gravity of 1860 (cf. chloroform 1500), a boiling-point of 51° C., and a sweetish odour not unlike that of chloroform. Chemically, it is a halogenated ethane with the structural formula

Clinical Trials

Fluothane has been administered as the sole or the principal anaesthetic agent to a number of volunteers and to 310 patients (varying in age from 7 months to 91 years) for a variety of surgical procedures (lasting from 3 to 150 minutes). There were no deaths under anaesthesia in the series, although many of the patients came to operation in a poor physical state. The pre-operative conditions included diabetes, obstructive jaundice, cardiac failure, thyrotoxicosis, and asthma, but none were affected adversely by the anaesthetic.

One patient died during the post-operative period, but this was probably not attributable to the anaesthetic.

An 84-year-old man received open drop fluothane for the amputation of a gangrenous toe. The administration was uneventful and lasted for 15 minutes. The patient recovered consciousness before leaving the operating theatre and was quite well for the next four days. He then became increasingly irrational, developed bronchopneumonia, and died on the seventh post-operative day.

The object of this investigation was to confirm the promising results obtained in animal trials; to ascertain in humans the effect of known concentrations of fluothane vapour; and to exploit the administration of the drug by simple methods.

Methods of Administration

Since it was known that the administration of fluothane in conjunction with nitrous oxide and oxygen from a standard Boyle apparatus was being investigated elsewhere (Johnstone, 1956), we have limited our attention to the administration of the drug by the "open drop" method and by its use in an E.M.O. inhaler (Epstein and Macintosh, 1956) modified and calibrated to deliver known concentrations of fluothane vapour in air. In this way it has been possible to observe the action of fluothane without the complication of other anaesthetic agents, and to obtain an im-

pression of the effects produced by known concentrations of the agent.

Open Drop Induction.—Fluothane has been administered by the open drop method to 63 patients and to a further 29 after the preliminary injection of a "sleep" dose of thiopentone (rarely more than 0.2 g.). In most instances, induction was smooth and pleasant, producing unconsciousness in about one minute. Swallowing during induction was not uncommon, but this did not interfere with the administration and was not followed by vomiting. Coughing was rare and was always relieved by raising the mask. Struggling and breath-holding were unusual. Surgical intervention could often be tolerated after three to four minutes, although a further eight to ten minutes was necessary if the surgical stimulus was to be severe. We found that the rate of drop should be somewhat faster than when chloroform is administered, but otherwise the same general principles should be followed—that is, the head turned to one side and no Gamgee tissue placed between the face and mask. In 58 cases open drop anaesthesia was maintained throughout the operation. In 31 other cases open drop induction was followed by maintenance with the inhaler.

Fluothane Calibrated E.M.O. Inhaler.—Twenty-three cases were induced with the inhaler without the preliminary injection of thiopentone. Induction was slightly slower than with the open drop method, and an excitement stage was seen rather more often; but in either case a small preliminary dose of thiopentone makes induction smoother and pleasanter for the patient. An advantage in using the inhaler and its associated bellows (Macintosh, 1953) is the ease with which respiration can be assisted or controlled. When respiration is depressed from any cause the bellows is a great help in ensuring efficient respiratory exchange.

Anaesthetic Concentrations of Fluothane

The concentrations of fluothane required to produce certain effects were tested on volunteers, and these findings were confirmed in clinical practice.

The inhalation by volunteers of 0.5% fluothane in air (v/v) for periods up to five minutes did not produce unconsciousness. In most instances the subjects noticed flushing of the face and a general sensation of warmth after 10–12 breaths, and shortly afterwards sounds became accentuated. There was no "muffling" or the effect of distance so common during the inhalation of weak mixtures of nitrous oxide or trichlorethylene. There was a slight reduction in sensation to pin-prick after one minute, but this was not considered to be of clinical value. Even after continuous inhalation for five minutes it is doubtful whether any worth-while analgesia was produced.

In volunteers the inhalation of 1% fluothane in air invariably produced loss of consciousness. The onset of a light level of unconsciousness usually occurred in the second minute, and the depth did not alter appreciably during a further four minutes' inhalation. Volunteers were unaware of painful stimulation during this period, although it often increased the rate or depth of respiration. Consciousness was regained almost as soon as the mask was removed and mental alertness returned rapidly. A not unpleasant sensation of lassitude persisted for a further two to three minutes, after which the subject could sit and stand unaided. Most, however, complained of diplopia during this period, even though other muscle activity seemed to have returned to normal. Dryness of the mouth was often noticed for a further 15–20 minutes, but there were no other unpleasant sequelae.

Concentrations of up to 1.5% fluothane in air were well tolerated by all volunteers and evoked no unpleasant sensations of suffocation or irritation of the respiratory tract.

In most patients 2% fluothane in air provided a satisfactory level of surgical anaesthesia, although it was necessary to administer 3% for short periods to robust subjects and those in whom an extreme degree of relaxation was necessary.

*The trade name given by Imperial Chemical Industries to 2-bromo-2-chloro-1,1,1-trifluoro-ethane. The drug is not yet freely available.

Airway

Although the majority of our patients received some form of premedication, 20 cases did not have atropine. Even in these, the absence of pharyngeal secretions was noticeable.

There was rapid relaxation of the masseter muscles and a depression of the pharyngeal reflexes: an oral airway was therefore tolerated early. A laryngoscope blade could be introduced after four to five minutes, although the passage of an endotracheal tube usually required a further three to four minutes of anaesthesia. Even when intubation was attempted at a light level of anaesthesia, laryngeal spasm was short-lived and was more commonly an adduction of the cords rather than true spasm. It was therefore possible to cocaineize the cords at an early stage, thus facilitating the introduction of a tube within five to six minutes of the beginning of an administration without response. Out of a total of 132 patients who were intubated, less than half received succinylcholine chloride for this purpose, and even then its use was usually dictated by the demands for speed during long surgical lists.

Premedication

Several combinations of drugs for premedication were used in this series:

No premedication	..	..	..	..	..	..	8
Atropine only	..	..	..	..	..	..	27
Morphine and atropine	..	..	..	..	..	..	28
"Omnopon" and scopolamine	..	..	..	..	..	..	135
Pethidine and atropine	..	..	..	..	..	..	66
Others (barbiturates, barbiturates and atropine, etc.)	..	..	..	..	..	..	46
							310

If respiration is not to be assisted or controlled, we are impressed by the advantages of using "light" premedication, which avoids undue respiratory depression. Thus, in patients who received atropine only, or pethidine (50 mg.) and atropine, induction was smooth and rapid; moreover, recovery was not delayed. We advise that drugs with a marked central respiratory depressant effect should not be given within one and a half hours of the induction of anaesthesia.

Effect on Cardiovascular System

We have come to expect a slowing of the pulse under this anaesthetic, and rates of 60-70 were common soon after induction. The pulse rate appears to fall as the depth of anaesthesia increases, and on occasion we have observed rates as low as 40 a minute. To some extent, atropine counteracts this effect, and on these grounds we believe that premedication with atropine is advisable although not essential.

Patients with cardiac irregularities were anaesthetized without alteration in their rhythm. Dropped beats persisting for periods of about two minutes were observed in two patients during anaesthesia. They occurred after unwise attempts at intubation under very light anaesthesia which provoked vigorous bouts of coughing and breath-holding. The irregularities might well have been provoked by a similar insult under light anaesthesia with any other agent.

A fall in blood pressure was common, and systolic pressures in the region of 90 mm. Hg were usual within five minutes of starting an administration, and occurred both with and without the preliminary administration of thiopentone. Just as the pulse rate tended to slow with deeper anaesthesia, so also did the blood pressure tend to fall, but we found experimentally that as a rule this could be reversed by the administration of atropine or methylamphetamine. The consequent dry, bloodless operating field is similar to that obtained with hypotension deliberately induced by other methods. With the exception of a brief period of mental confusion in one elderly patient, no ill-effects were seen from either the slow pulse or the low blood pressure.

Respiratory System

Concentrations of 1% fluothane and higher caused well-marked changes in the character of respiration. During light anaesthesia in volunteers breathing 1% fluothane in air the rate generally increased or stayed within a range of 18-24 a minute. On a few occasions the rate fell to 4-6 a minute. In patients undergoing surgical stimulation these slow rates were never seen: 30 a minute was common, and we considered this normal, but higher rates were observed on occasion.

In both volunteers and patients the depth of respiration decreased whenever the rate increased or remained normal. This was apparent clinically, although it was not until the volume of inspired gases was measured with a spirometer that the full extent of the respiratory depression was appreciated. Neither the rate nor the depth of respiration could be related to the depth of anaesthesia, and thus these signs of anaesthesia, so well recognized with many other anaesthetic agents, became meaningless. As is to be expected, surgical stimulation during light anaesthesia increased the rate and depth of respiration, but even in these circumstances the minute-volumes recorded were much below the expected values. Thus a recording as low as 1.2 litres a minute was made in one volunteer after breathing 1% fluothane in air for only three minutes, while several of our patients gave readings of 3-4 litres a minute during the course of an operation.

With such a degree of respiratory depression, cyanosis was seen frequently unless respiration was assisted or oxygen added to the inspired mixture, and in the second alternative carbon dioxide retention might be occurring insidiously. Such degrees of respiratory depression also limit the depth of anaesthesia obtainable during spontaneous respiration using either the open drop technique or a draw-over inhaler. Thus it may become necessary to assist or control respiration to circumvent these hazards. By increasing the respiratory exchange at the end of an administration it is possible to excrete fluothane at an increased rate and thus hasten recovery.

Under fluothane/air anaesthesia, respiration was usually smooth, quiet, and regular. No irritation is caused to the respiratory tract, and it was therefore possible to control respiration with the greatest of ease.

Occasionally, however (in 12 cases), the induction was interrupted by periods of apnoea, sometimes lasting for one to two minutes. These never occurred after induction with thiopentone nor after the second minute of inhalation. The apnoea differed from active breath-holding in that inflation could still be performed with perfect ease. Spontaneous respiration usually restarted after applying a painful stimulus to the patient. No explanation can be offered for this phenomenon, although it occurred with remarkable frequency in previous experiments on dogs (A. B. Bull, 1955, personal communication).

Muscular Relaxation

On occasion it was difficult to achieve an adequate degree of muscular relaxation while respiration was spontaneous. On the other hand, respiration could be controlled easily, and it then became possible to provide adequate conditions for surgery quickly in most cases. This suggests that fluothane behaves in a similar manner to cyclopropane in that a quiet, depressed respiration limits the intake of the agent and thus the depth of anaesthesia.

An additional factor occurs when the E.M.O. or other inhaler with similar characteristics is being used. Such inhalers operate efficiently within certain ranges of inspiratory flow rates (usually about 7-12 litres a minute). If the flow rate falls below this range, so also does the concentration of vapour leaving the inhaler, and these circumstances were experienced in our series when low inspiratory minute-volumes were demonstrated.

During intra-abdominal operations in which muscular relaxation was adequate, peristalsis was seen on several occasions.

Use of Muscle Relaxants

Succinylcholine chloride was administered (20–100 mg.) to 68 patients under fluothane anaesthesia. The effects were identical to those seen when this muscle relaxant is used with other anaesthetic agents.

Twenty patients received gallamine triethiodide, and, in view of reports suggesting that profound blood-pressure and pulse-rate changes might be expected with the use of relaxants, it was given with caution. Injections of 40 mg. caused the usual slight rise in pulse rate, and little or no change in the blood pressure. Larger doses (up to 120 mg.) sometimes caused a slight fall in blood pressure, although this was no more pronounced than that to be expected with fluothane by itself.

On the other hand, when neostigmine was used at the end of the operation to counteract the effect of any residual gallamine triethiodide bradycardia was particularly noticeable. Preliminary doses of atropine should therefore be greater than the usual 1/100 gr. (0.65 mg.). When doses of 1/75–1/50 gr. (0.97–1.3 mg.) were used severe bradycardia was avoided, but we would stress the advisability of giving neostigmine cautiously, and in divided doses (0.5 mg. at a time, with a total dose not exceeding 2.5 mg.).

D-Tubocurarine was administered in doses of 7.5–15 mg. to 20 patients. More than half showed little or no change in their blood pressures despite the use of controlled respiration. However, in some, particularly the elderly, there was a fall in blood pressure of 30 mm. Hg or more. When spontaneous respiration remained, this fall was not serious, but it was frequently aggravated by the establishment of controlled respiration. Thus in a 77-year-old man with a pre-operative blood pressure of 220/105, a systolic pressure of 45 mm. Hg was recorded 15 minutes after the injection of 10 mg. of D-tubocurarine with subsequent control of respiration. However, the patient looked well and the blood pressure started to rise as spontaneous respiration returned. With one exception, the general appearance of all these patients was satisfactory:

A 45-year-old woman undergoing vaginal hysterectomy received thiopentone, 0.25 g., followed by 2% fluothane/air from the inhaler. After intubation, 15 mg. of D-tubocurarine was injected and respiration controlled with 1% fluothane. Ten minutes later her systolic pressure had fallen from 145 mm. Hg to 55. Her pulse rate was 64 and she appeared pale and slightly cyanosed. Atropine, 1/50 gr. (1.3 mg.) raised her pulse rate to 120 without affecting the blood pressure. Neostigmine in divided doses raised her systolic pressure to 75 mm. Hg before spontaneous respiration restarted and her colour improved. The patient made a satisfactory recovery.

Thus, in view of the profound changes which may occur on occasion, further investigation is required on the use of muscle relaxants and in particular D-tubocurarine during fluothane anaesthesia.

One patient who was receiving mephenesin in the course of the treatment of tetanus was anaesthetized with fluothane/air without any unusual response.

Recovery

Consciousness may be expected to return within ten minutes of stopping the administration. However, depressed respiration due either to the fluothane itself or to unnecessarily heavy premedication increased the time interval by as much as three-quarters of an hour in 15% of our cases.

Nausea and vomiting were strikingly rare, and most patients stated that they felt very fit. The rapid return of mental alertness has already been mentioned. Apart from a few frontal headaches—which may well have been co-

incidental—only two attributable post-anaesthetic sequelae were observed in this series:

Shivering.—Fourteen patients had generalized attacks of shivering as consciousness was returning. These were sometimes quite violent and lasted three to four minutes.

Restlessness.—Six children were confused and restless for up to an hour after return to bed. This might be due to a rapid recovery from the anaesthetic, with no residual analgesia while the effect of a barbiturate premedication still persisted. Restlessness did not occur when an analgesic was administered soon after the return of consciousness.

Effect on Sympathetic Nervous System

As a rule, a flush starts in the face and neck within the first minute of the administration and the skin feels warm to the touch. Later there is a noticeable injection of the conjunctivae and the superficial veins become prominent. Sweating is absent or minimal, and when present there was usually an accompanying respiratory depression, so that the cause might well have been carbon dioxide retention.

Miscellaneous Observations

From the evidence of volunteers, fluothane appears to have little value as an analgesic agent. Loss of consciousness occurs before there is any appreciable diminution in sensitivity.

Fluothane has been spilt in the eyes inadvertently. No harm resulted, although the response by a lightly anaesthetized subject was vigorous.

Solutions of adrenaline in which the total dose did not exceed 0.5 ml. (1/1,000 concentration) were injected subcutaneously into 14 patients to provide haemostasis (thyroidectomy, mastoidectomy, and antrostomy). The only noticeable response was a small rise of pulse rate in two cases.

On 19 occasions fluothane was employed as an induction agent before administering ether. The change-over was always effected rapidly and smoothly, and was followed by a rise of pulse rate and blood pressure to normal.

Under ideal conditions, fluothane is a stable compound, but in the presence of air, moisture, and light it can decompose slowly into the various acids of the halide group. In consequence, the drug should be stored in a cool place in amber-tinted bottles. These decomposition products can affect some metals, including tin and aluminium, both of which may be found in everyday modern anaesthetic apparatus. In addition, fluothane may be taken up by rubber, causing it to soften and to swell. The rubber reverts slowly to its previous state when exposed to air. This effect has been noted on the standard rubber corks found in drop-bottles, and in the corrugated hose of anaesthetic apparatus, which then tends to slip from metal connexions. We have seen no adverse effects on patients attributable to decomposition products, but on theoretical grounds one should bear in mind the toxic effects of these acids.

Conclusions

Fluothane is a volatile anaesthetic agent which, like ether, can be administered by the simplest possible methods. It has the advantage of being both non-flammable and non-explosive.

Since it does not stimulate pharyngeal secretions, premedication with atropine is not essential: on the other hand, atropine is advisable to counteract the marked bradycardia encountered in deep and protracted anaesthesia.

Induction is smooth, rapid, and not unpleasant even by the open drop technique. Recovery is similarly rapid and unassociated with unpleasant complications.

The range of anaesthetic concentrations lies between 1 and 3% fluothane in air, and within these limits adequate conditions can be provided for most types of

surgery. Unfortunately, few upper abdominal cases were encountered, and in these the muscular relaxation was not always perfect. The fault here may well have been due to our inexperience in the use of this new drug.

Fluothane causes a slowing of the pulse rate and a fall in blood pressure in most instances, but these do not appear to be harmful. In fact, the hypotension has often been appreciated by the surgeon, who has remarked on the dry operating field. Excessive falls in blood pressure or pulse rate can quickly be treated by the injection of atropine or methyl amphetamine, or the administration of ether.

The greatest disadvantage exhibited by fluothane is the depression of respiration which occurs not infrequently and may be sufficient to cause cyanosis and CO_2 retention. These undesirable features may be overcome by assisting or controlling respiration, which will also enable greater depths of anaesthesia to be obtained and thereby increase the scope of this agent.

In our opinion, this disadvantage is great enough to warrant limiting the use of the agent to all but skilled anaesthetists until more is known about its properties. It is possible that the disturbances of respiration which we encountered can be avoided by refinements in technique. If this is so, we believe that fluothane may become a valuable anaesthetic agent with a wide variety of uses. By virtue of its non-flammability and the simple method by which it can be administered, it could then attract the general practitioner for use in minor operations, provided he is equipped to treat the respiratory depression which may be encountered. Because of its flexibility it may be preferable to trichlorethylene except in respect of its analgesic properties. Indeed, with the high cardiac safety factor which has been suggested (Johnstone, 1956) fluothane compares advantageously with chloroform.

The pleasant and rapid induction is of particular value in children. A smooth change-over to ether can be effected if required, but when used as the sole anaesthetic agent it provides uniformly good muscular relaxation.

We wish to express our gratitude to Imperial Chemical Industries for the supplies of fluothane; to Dr. H. G. Epstein for his willing help and assistance in matters relating to the inhalers; and to Sir Robert Macintosh for his encouragement and advice.

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The General Council of the Press, at its meeting on October 17, considered a complaint from the Town Clerk of Ayr against the *Sunday Mail* of Glasgow in respect of an article about a visit to the Ayr Welfare Home and Hospital. The ground of the complaint was that the article would create a false impression of the institution. The editor had refused to publish any withdrawal of the allegations and criticism because he was satisfied that the article was fair comment on a matter of public importance. The Council expressed the view that the *Sunday Mail* had approached the matter in a responsible manner and held that the article was fair comment on a matter of public interest.

THE PHYSIOLOGICAL CASTRATION SYNDROME IN BREAST CANCER

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The treatment of metastatic breast cancer is still rather empirical. It can be put finally on a scientific basis only when specific tests for the various factors which influence the growth of breast cancer can be easily performed. At present, however, clinical observation of these cases under treatment can yield valuable information on the course of the disease.

This paper describes clinical observations on a series of cases of metastatic breast cancer treated by a variety of methods. An overall picture of the course of the disease is available, as they are for the most part completed cases.

Introduction

Scowen (1955), in his Langdon-Brown lecture at the Royal College of Physicians in 1955, showed from his experience that the occurrence, either naturally or artificially, of the menopausal state was one of the main factors in regression of tumour growth. This state is manifested by a fall in oestrogen production and change of function of the anterior lobe of the pituitary with a great rise in gonadotrophin activity. It was suggested that the regression probably resulted from a combination of these circumstances rather than a simple oestrogen withdrawal, and that the conception of simple oestrogen dependence could not be fully substantiated.

At some time, from a matter of months to five years, after the menopause the oestrogen level rose and the gonadotrophin fell, giving a pattern similar to the pre-menopausal state. At this stage progress of the growth of metastatic breast cancer occurred, as it did before the menopause. The induction of a further menopausal state by adrenalectomy at this time caused a further regression of the growth.

This sequence of changes is summarized by the accompanying diagram (Scowen, 1955) which shows the classical effect

Diagram showing the commonest menopausal pattern induced by castration or occurring naturally. A further follow-up of this shows a reversal to the pre-menopausal state.

of a castration or the menopause, followed later by a reversal to the pre-menopausal state but without menstrual bleeding. Although true for the majority of cases, there were a few patients who did not follow this pattern.

All the patients in our series developed a carcinoma in the pre-menopausal period. It has been shown by Clemmesen (1948), Clemmesen and Busk (1949), and Anderson *et al.* (1950) that there are two peaks of incidence in breast cancer. They occur roughly in the five-year periods before and after the menopause. It would seem that the fall in incidence of breast cancer at the menopause occurs with the consequent drop in oestrogenic activity at this time. Of course this can influence only those carcinomata which are primarily hormone-dependent, and so generally affects only about 45% of the patients.