EVALUATION OF INHALERS FOR TRICHLOROETHYLENE, CHLOROFORM AND FLUOTHANE

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Consideration of the medical management of mass casualties spotlights the need for development of methods for the administration of analgesic and anesthetic drugs to the largest possible number of injured persons. Assuming that there will be a tremendous disparity between the number of casualties and the available professional medical care, pain relief for surgical procedures would of necessity be provided by self administration or by briefly trained field personnel. Therefore, a study was initiated to explore the analgesic properties of certain nonflammable inhalation agents and the means whereby their administration could be safely accomplished under such circumstances.

Inhalers for the induction and maintenance of chloroform anesthesia were developed shortly after the introduction of chloroform as an anesthetic agent. To control the vapor concentration one of two principles was utilized. One was that of vaporizing a known amount of liquid in a given space as in Clover's chloroform apparatus (1). The other was the draw-over method, that of diversion of a variable portion of inspired air through a vaporizing chamber. An early example of this was the chloroform inhaler designed by Levy in 1904 (2). In the 1940's when the analgesic properties of trichloroethylene were being explored, a number of inhalers were developed. These vary in design and control mechanism, as well as in their size and weight. They all utilize the draw-over principle. The characteristics of these inhalers which make it possible to deliver a constant concentration of anesthetic vapor under a variety of circumstances appear to be highly desirable. This is especially true when the anesthetic agent is to be self administered or administered by personnel other than trained anesthetists.

In the course of evaluating trichloroethylene, chloroform and Fluothane a series of inhalers was tested. This was the preliminary phase of the study of chloroform and Fluothane "analgesia" in experimental animals and in man. A method of analysis with an infrared spectro-

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photometer was used to monitor the concentration of anesthetic mixtures as delivered from the inhalers.

Methods

A Perkin-Elmer double beam recording infrared spectrophotometer (Model 21) was used for the analysis of vapor concentrations of trichloroethylene, chloroform, and Fluothane. Each agent was introduced into an evacuated 10 cm. gas sampling cell and scanned to obtain an infrared absorption spectrum of the vapor. From the spectrum

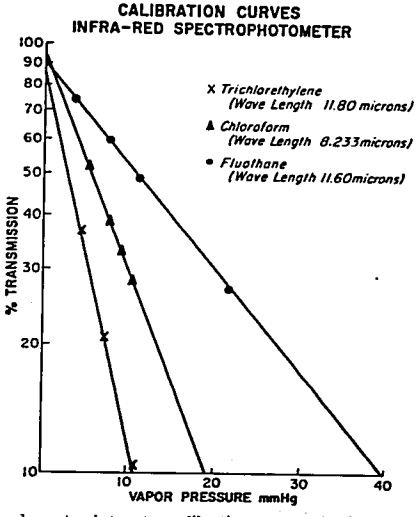

Fig. 1. Infrared spectrophotometer calibration curves of trichloroethylene, chloroform and Fluothane vapor at their respective wave lengths of measurement. Per cent transmission was plotted on log scale. From vapor pressure, vapor concentration in volumes per cent was calculated.

a wave length was selected at which the change in transmittance was a maximum for a change in vapor pressure. In the case of trichloroethylene this was 11.80 microns; for chloroform, 8.233 microns; and for Fluothane, 11.60 microns. A calibration curve of log per cent transmission versus vapor pressure was obtained for each agent at its respective wave length of measurement. With all three agents the calibration curves were linear (fig. 1).

For evaluation of an inhaler the apparatus was charged with one of three agents. A Bird respirator pump was used to draw the anes-

thetic mixture from the inhaler. The tidal volume and stroke frequency of the pump were varied independently. The infrared sampling cell was placed between the inhaler and the pump so that all of the mixture was channeled through the sampling cell. With the wave length of measurement set according to that used for calibration for each particular agent, the per cent transmittance of the mixture was recorded continuously. From the per cent transmittance, vapor pressure was obtained from the calibration curve. Vapor concentration, in turn, was calculated from the vapor pressure and barometric pressure.

Six inhalers were evaluated. These were: the Duke inhaler, a modified Duke inhaler, the Emotril inhaler,* the Tecota inhaler,† the Airlene inhaler, and an experimental Tecota chloroform inhaler.† Each inhaler was tested with one, two, or three of the anesthetic agents under consideration. Vapor concentration of each agent in the mixture delivered from the inhaler in relation to the tidal volume, the stroke frequency of the respirator, and the available settings provided on the inhaler, was determined. In addition, the ability of the inhaler to maintain a given concentration over a period of time was also tested.

Results

Duke Inhaler.—This inhaler was developed at the Duke University for use with trichloroethylene (3). The performance of this inhaler was evaluated by Hall *et al.* (4) and compared with that of the Cyprane and McGill inhalers using an interferometer for the analysis of vapor concentration. It is approved by the Council on Physical Medicine and Rehabilitation of the American Medical Association as an apparatus suitable for the administration of trichloroethylene for analgesic purposes (5). In the present study the inhaler was filled and held in vertical or horizontal position on a laboratory stand. The oxygen inlet was unstoppered. Trichloroethylene vapor concentrations as delivered from the inhaler with a minute volume of 8 l. are shown in table 1. A minute volume of 10 l. increased the vapor concentrations slightly; when the minute volume was 6 l. or less, the vapor concentration dropped.

With chloroform the vapor concentrations at various settings are also shown in table 1. They varied from 0.00 per cent at minimum setting to 2.12 per cent at setting 6.

Modified Duke Inhaler.—It appeared that chloroform vapor concentration as delivered from the Duke inhaler is too high if chloroform is to be used for analgesic purposes in this fashion. In order to adapt the Duke inhaler for use with chloroform it was modified to compensate

* The Emotril inhaler was made available by Anesco of Stratford, Conn., distributor for Medical and Industrial Equipment, Ltd., London, England.

† The Tecota Mark VI and the experimental chloroform inhaler were made available by Canam Company of Toronto, Canada, representing Cyprane, Ltd., of Great Britain. The experimental model was especially calibrated for use with chloroform through the courtesy of Mr. Fraser Sweatman of Canam Company and Mr. Edmondson of Cyprane, Ltd.

TABLE 1

CONCENTRATIONS OF TRICHLOROETHYLENE AND CHLOROFORM VAPOR IN VOLUME PER CENT WITH DUKE INHALER (STROKE VOLUME, 400 CC.; FREQUENCY, 20/MINUTE)

	Setting						
	Minimum	2	3	4	5	6	Maximum
Trichlorethylene							
Manufacturer's data	0.32	0.57	0.75	0.80	0.86	0.92	1.09
Inhaler vertical	0.00	0.16	0.48	0.72	0.96	1.10	1.17
Inhaler horizontal	0.10	0.53	0.62	0.88	1.02	1.12	1.15
Chloroform							
Without cap	0.00	0.68	1.12	1.65	1.83	2.12	—
With cap, opening 1	0.00	0.44	0.68	1.02	1.26	1.59	—

for the lower boiling point of this agent. A metal cap with various sized openings was made to put over the bottom of the inhaler to reduce the air flow through the vaporizing chamber. As shown in table 1, when this metal cap was in place, the chloroform vapor concentration decreased considerably, but the increment with each successively higher setting still appeared to be too great. Therefore, in addition, the outlet port in the head of the inhaler was reoriented so that the long axis of the port became parallel with that of the inhaler (fig. 2). Thus, movement of the regulator along the scale alters the air flow ratio relatively less than with the original design. With the inhaler thus modified, it has nine positions for the regulator instead of seven. The metal cap has 6 openings, the diameter of which are 3, 4, 5, 6.5, 8 and 9.5 mm. Therefore, with the metal cap in place there are 54 possible combinations.

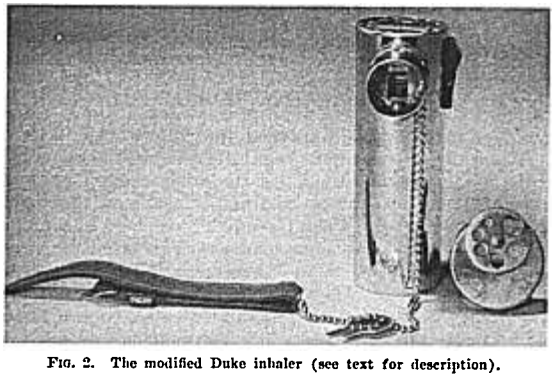

FIG. 2. The modified Duke inhaler (see text for description).

When charged with trichloroethylene and tested without the metal cap in place, the inhaler delivered 0.00 per cent of vapor at setting 1 and 0.98 per cent at setting 9. The increment of vapor concentration with each successive setting is less than that with the Duke inhaler (table 2).

When tested with chloroform, the vapor concentration varied between 0.00 per cent with the minimum setting and smallest opening to 1.66 per cent with the maximum setting and the largest opening. As shown in table 2, small changes of vapor concentrations were obtained by moving the regulator or by changing the openings on the metal cap. As in the case of the Duke inhaler, vapor concentrations dropped sig-

TABLE 2

CONCENTRATIONS OF TRICHLOROETHYLENE, CHLOROFORM AND FLUOTHANE VAPOR IN VOLUME PER CENT WITH MODIFIED DUKE INHALER (STROKE VOLUME, 400 CC.; FREQUENCY, 20/MINUTE)

	Setting								
	1	2	3	4	5	6	7	8	9
Trichlorethylene Without cap	0	0.10	0.18	0.23	0.29	0.40	0.53	0.76	0.98
Chloroform									
Cap opening 1	0	0.13	0.42	0.57	0.60	0.70	0.77	0.88	1.02
Cap opening 2	0	0.14	0.44	0.61	0.68	0.82	0.97	1.02	1.19
Cap opening 3	0	0.15	0.46	0.63	0.70	0.97	1.10	1.17	1.34
Cap opening 4	0	0.17	0.49	0.66	0.80	1.08	1.28	1.32	1.52
Cap opening 5	0	0.17	0.49	0.69	0.87	1.13	1.33	1.36	1.60
Cap opening 6	0	0.17	0.49	0.71	0.92	1.17	1.36	1.40	1.66
Fluothane									
Cap opening 1	0	0.08	0.30	0.50	0.58	0.70	0.82	1.00	1.27
Cap opening 2	0	0.08	0.42	0.55	0.69	0.84	0.95	1.10	1.45
Cap opening 3	0	0.08	0.45	0.59	0.79	0.99	1.07	1.20	1.40
Cap opening 4	0	0.09	0.49	0.64	0.89	1.07	1.17	1.35	1.55
Cap opening 5	0	0.13	0.52	0.70	0.95	1.15	1.18	1.39	1.55
Cap opening 6	0	0.13	0.52	0.72	0.91	1.16	1.14	1.39	1.63

nificantly when the minute volume was less than 6 liters. Change of position of the inhaler also influenced the chloroform vapor concentration. When the setting of the regulator, size of the opening on the cap, and the minute volume remained the same, changing the position of the inhaler from vertical to horizontal increased the vapor concentration by 0.3 per cent. When the inhaler was held by hand, instead of by a laboratory stand, the same maneuver increased the vapor concentration by 0.9 per cent. Vapor concentrations of Fluothane are also presented in table 2. They varied from 0.00 per cent to 1.63 per cent. The ability of the inhaler to maintain vapor concentration over a period of time is shown in figure 3. The inhaler was filled with 15 cc. of the agent and the respirator pump was set to draw 10 l. per

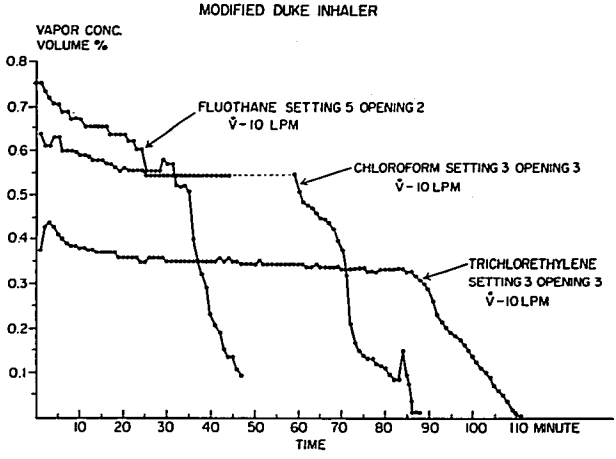

FIG. 3. Vapor concentrations of trichloroethylene, chloroform, and Fluothane as delivered from the modified Duke inhaler in relation to time. Fifteen cubic centimeters of each of the agents was used to fill the inhaler.

minute. The vapor concentrations were determined continuously until the inhaler was exhausted. Vapor concentrations of chloroform and trichloroethylene were maintained at a constant level. The result with Fluothane was less satisfactory.

Emotril Inhaler.—This inhaler was developed by Epstein and Macintosh of Oxford, England, for use with trichloroethylene (6). It

TABLE 3

CONCENTRATIONS OF TRICHLOROETHYLENE, CHLOROFORM AND FLUOTHANE VAPOR IN VOLUME PER CENT WITH EMOTRIL INHALER
(STROKE FREQUENCY 20/MINUTE)

	Stroke Volume (cc.)			
	200	300	400	500
Trichlorethylene				
"Weak"	0.16	0.28	0.29	0.32
"Normal"	0.33	0.41	0.42	0.47
Chloroform				
"Weak"	0.58	0.80	0.81	0.86
"Normal"	1.00	1.23	1.21	1.20
Fluothane				
"Weak"	0.19	0.31	0.34	0.43
"Normal"	0.38	0.56	0.67	0.80

is a draw-over type inhaler with 2 air intake openings, one for bypass air and the other for air passing through the vaporizing chamber. The vaporizing chamber has a capacity of 60 cc. of liquid and contains a large wick, affording a large surface area for vaporization. The vaporizing chamber opens into the by-pass air stream through a port which is controlled in size by a thermocompensating mechanism. This aids in maintaining a constant vapor concentration over a wide range of ambient temperature (12 to 27 C.). The outlet of the inhaler is equipped with a nonrebreathing valve. From the outlet a length of

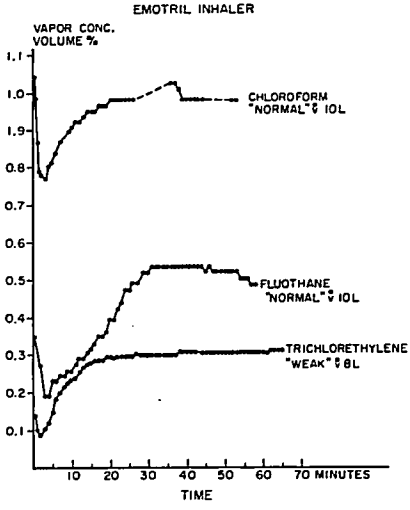

FIG. 4. Vapor concentrations of trichloroethylene, chloroform and Fluothane as delivered from the Emotril inhaler in relation to time. Thirty to forty cubic centimeters of each of the agents was used to fill the inhaler. Note the initial low values and time required for the vapor concentrations to become stabilized. Filling the inhaler during operation did not alter the vapor concentration.

corrugated tube leads to the face mask. A spring loaded valve for expiration is located in the connecting metal piece. There are two settings available on the inhaler, "normal" and "weak." The "weak" setting allows additional air dilution of the anesthetic mixture. The inhaler is calibrated to deliver 0.5 per cent of trichloroethylene vapor at "normal" setting and 0.35 per cent at "weak" setting.

Using the infrared spectrophotometric method of measurement above described, this inhaler was found to deliver 0.43–0.49 per cent of trichloroethylene at "normal" setting and 0.27–0.33 per cent at "weak"

setting with a minute volume of 8–10 liters. With chloroform the vapor concentrations varied widely: 1.0–1.3 per cent at "normal" and 0.70–0.95 per cent at "weak" setting. When filled with Fluothane the vapor concentrations were 0.50–0.80 per cent at "normal" and 0.33–0.53 per cent at "weak" setting. With minute volumes of less than 6 l. the vapor concentrations decreased. This was observed with all 3 agents tested. Table 3 shows the average vapor concentrations obtained under these conditions.

This inhaler showed one feature which appears to be undesirable. During the course of evaluating its ability to maintain a given vapor concentration, it was noted that the vapor concentrations did not become stabilized until 15–30 minutes after the start of operation. The initial concentrations were considerably lower than those obtained after stabilization (fig. 4).

TABLE 4

CONCENTRATIONS O: TRICHLOROETHYLENE, CHLOROFORM AND FLUOTHANE VAPOR IN VOLUME PER CENT WITH TECOTA INHALER (STROKE FREQUENCY 20/MINUTE)

	Stroke Volume (cc.)			
	200	300	400	500
Trichloroethylene				
"Minimum"	0.10	0.20	0.27	0.30
"Maximum"	0.34	0.43	0.48	0.48
Chloroform				
"Minimum"	0.46	0.64	0.71	0.75
"Maximum"	0.85	1.05	1.05	1.06
Fluothane				
"Minimum"	0.16	0.40	0.54	0.63
"Maximum"	0.52	0.83	0.92	1.00

Tecota Mark VI.—This inhaler was developed by Cyprane, Ltd., in England for use with trichloroethylene. This and the Emotril inhaler have been approved by the Central Midwives Board of Great Britain, mostly for use during home deliveries. It is of the draw-over type with a single air intake opening. The vaporizing chamber has a liquid capacity of about 40 cc. A control dial allows variations between minimum and maximum settings, and is calibrated to deliver 0.35 per cent of trichloroethylene at minimum and 0.5 per cent at maximum setting. The inhaler has a mechanism for thermocompensation and is equipped with nonrebreathing valves as well as a wide-bore breathing tube leading to the face mask.

Vapor concentrations of trichloroethylene, chloroform and Fluothane as delivered from the Tecota inhaler are presented in table 4. A minute volume of less than 6 l. caused a significant decrease in vapor concentrations. In contrast to the Emotril inhaler, when tested for

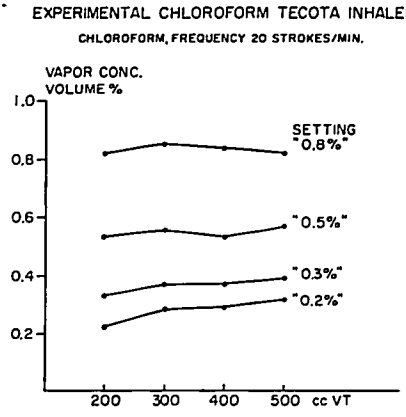

FIG. 5. Chloroform vapor concentrations as delivered from the experimental chloroform Tecota inhaler. Numbers below setting indicate calibration on the apparatus.

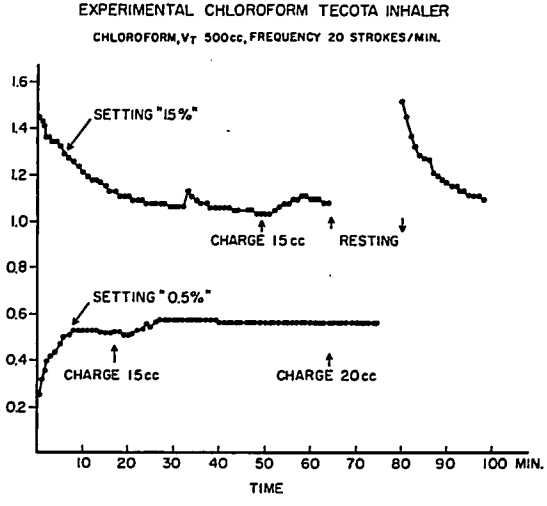

FIG. 6. Vapor concentrations of chloroform as delivered from the experimental chloroform Tecota inhaler in relation to time. Note the rapid fall in vapor concentrations when the inhaler was set at "1.5 per cent."

stability the vapor concentration became stabilized within the first few minutes and remained constant until the agent was nearly exhausted.

Experimental Tecota Chloroform Inhaler.—This inhaler is similar in design to the Tecota Mark VI, except that it is calibrated for use with chloroform. It has settings marked for 0.2, 0.3, 0.5, 0.8, 1.0, 1.5, and 2.0 per cent of chloroform vapor. Figure 5 shows the vapor concentrations of chloroform delivered when the inhaler was tested with the control set at "0.8 per cent" or lower. The vapor concentration delivered was quite stable (fig. 5). When the control was set at 1.0 per cent or above, the concentration could not be maintained and fell rapidly to a much lower level (fig. 6).

Variations in minute volume between 4 and 10 l. did not alter vapor concentrations significantly (fig. 5). In this respect, it seems that this inhaler is superior to the others tested.

TABLE 5

CONCENTRATIONS OF TRICHLOROETHYLENE AND CHLOROFORM VAPOR IN VOLUME PER CENT WITH AIRLENE INHALER (STROKE FREQUENCY 20/MINUTE)

	Stroke Volume (cc.)			
	200	300	400	500
Trichlorethylene				
"Low"	0.09	0.29	0.33	0.33
"Normal"	0.45	0.47	0.45	0.45
"High"	1.07	0.95	0.85	0.79
Chloroform				
"Low"	0.11	0.22	0.48	0.52
"Normal"	0.35	0.78	0.73	0.79
"High"	2.28	1.96	1.39	1.34

Airlene Inhaler.—This inhaler is manufactured by Airmed, Ltd. of London, England, for use with trichloroethylene. It is small and compact, comparable to the Duke inhaler in size and weight. It is also equipped with a thermocompensating mechanism. A number of small openings in the base of the inhaler allows air to flow through the vaporizing chamber. The size of the opening for the bypass air is regulated with a control knob on the mixture-adjusting collar marked "high," "normal," and "low." The inhaler is calibrated to deliver 1.0, 0.5, and 0.35 per cent of trichloroethylene at these settings.

The average vapor concentrations obtained when tested with trichloroethylene and chloroform are shown in table 5. Variations in the tidal volume altered the vapor concentrations in an irregular manner. When the tidal volume was reduced, vapor concentrations at "high" setting increased and that at "low" setting decreased. Also, the

vapor concentrations varied with different positions at which the inhaler was held. Because of the location of the bypass air opening, any air movement around the inhaler caused marked fluctuation in the vapor concentrations delivered.

Discussion

Infrared spectrophotometry is being used extensively in industry and in the laboratory for the analysis of liquid and gas samples. Recently it has been applied to the study of pulmonary function and of carbon dioxide homeostasis during anesthesia. As adapted for the present study, it proved to be very satisfactory in that it provided instantaneous sampling of anesthetic mixtures with accuracy and least effort. Changes in vapor concentrations in the magnitude of 0.01 per cent were easily measured. This seems to be adequate for the purpose of this investigation.

It appears that each one of the 6 inhalers thus evaluated has its own characteristics, many of which are desirable. The Duke inhaler and its modification are light and compact and generally performed in a satisfactory manner. The effect of position of these inhalers on the delivered vapor concentration may seem to be an objectionable feature. However, in their clinical use for trichloroethylene analgesia, the slight variation may not be of significance. With chloroform these variations were of considerable magnitude. The experimental circumstances may have contributed to this observation. During the expiratory phase, the valve in the respirator pump directed the air flow away from the inhaler. When the inhaler was held horizontally, the valve guarding the vaporizing chamber would remain open from gravitation. Thus, heavy anesthetic vapor would drift through the outlet port and increase its concentration. When used clinically, the reversed air flow during expiration probably would hold this valve in a closed position and variation in vapor concentration might not occur. Nevertheless, to eliminate this positional variation, provision can be made to mount the inhaler on a stand or any other available support in an upright position. By not holding the inhaler in the hand changes in vapor concentration due to body heat would be avoided. Such an arrangement is available with the Airlene inhaler.

The Emotril and the two Tecota inhalers are heavier units which rest on a broad base. A length of corrugated tubing leads from the unit to the face mask. They have a relatively large capacity for liquid agent to sustain vapor concentration for a long period of time. They are also equipped with thermocompensating mechanisms so that the vapor concentration would remain at calibrated levels when used in extreme climates. This seems to be a desirable feature, especially in field application, when the ambient temperature cannot be controlled.

With the Emotril inhaler vapor concentrations delivered during the first 15–30 minutes of operations were much lower than the stabil-

ized values. This phenomenon could be due to overcompensation by the thermocompensating device. However, since only one unit was tested, it cannot be stated with certainty that this is an inherent characteristic of inhalers of this design.

With the exception of the experimental chloroform Tecota inhaler, anesthetic vapor concentrations were sensitive to changes in minute volume. The clinical significance of this observation is unknown at present. The irregular response of vapor concentration to decreasing minute volume observed with the Airlene may not be desirable (table 5).

The modified Duke inhaler, the Tecota Mark VI, and the experimental chloroform Tecota inhaler were used extensively in animal experiments in this laboratory. In dogs paralyzed with succinylcholine and ventilated with a respirator, chloroform and Fluothane as delivered from these inhalers produced and maintained electroencephalographic patterns at levels 1, 2 or 3 (7) for periods up to 90 minutes. In a limited series of experiments in man these inhalers were used to administer chloroform to produce amnesia, analgesia and electroencephalographic changes to levels 1 or 2. The longest period of chloroform inhalation with this technique was 60 minutes. The subject remained conversant and cooperative throughout this period. It seems, therefore, that these inhalers are quite useful for the study of chloroform and Fluothane "analgesia."

The role of these inhalers in the anesthetic management of mass casualties would depend on a number of factors. The applicability and advisability of using chloroform and Fluothane for "analgesic" purposes cannot be determined without further studies. If the use of these drugs should prove to be advisable, an accurately calibrated inhaler would provide a practical and relatively safe method for administration. In untrained hands, an inhaler which is able to deliver controlled concentrations of anesthetic agents would minimize at least one of the anesthetic hazards, namely, overdosage. Waters (8) stated in the conclusions of the monograph on chloroform that "to discover a means of vaporizing chloroform under absolute control of the pressure of vapor which enters the patient's lungs is, in our estimation, a highly desirable accomplishment which ought most earnestly be sought." Some of the inhalers evaluated in this study may partly fulfill this objective.

Summary

The Duke inhaler, a modified Duke inhaler, the Emotril inhaler, the Tecota inhaler, the Airlene inhaler and an experimental Tecota chloroform inhaler were evaluated for use with trichloroethylene, chloroform and Fluothane. Vapor concentrations of these agents as delivered from these inhalers at different settings were measured. In addition the effect of changes in minute volume and the ability of the inhalers to maintain a given vapor concentration were also tested.

Measurement of vapor concentration was accomplished with the aid of a double beam infrared spectrophotometer.

The Duke inhaler performed satisfactorily with trichloroethylene. The modified Duke inhaler allowed a gradual increase in vapor concentration with each higher setting, thus made it suitable for use with chloroform. However, the inhaler's position and temperature had significant effect on the vapor concentration. With the exception of the experimental Tecota inhaler vapor concentration decreased when the minute volume was less than 6 or 8 liters. With the Airlene inhaler changes in minute volume caused irregular changes in vapor concentrations. All inhalers could maintain vapor concentration well except that with the Emotril inhaler a 20–30 minute period was necessary for the vapor concentration to become stabilized.

The Tecota inhaler and the experimental Tecota inhaler were used for the study of chloroform "analgesia" in experimental animals and in man and were found to be satisfactory.

The Fluothane used in this study was supplied by Ayerst Laboratories, Inc., New York, New York.

This study was presented on the "Work in Progress" program at the annual meeting of the American Society of Anesthesiologists, Los Angeles, California, October 17, 1957, and an abstract was published in ANESTHESIOLOGY, 19: 109, 1958.

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