THE PRODUCTION OF LARYNGOSPASM IN THE CAT BY VOLATILE ANAESTHETIC AGENTS

BY

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SUMMARY

Laryngospasm and apnoea or alterations in the rhythm of respiration have been produced in decerebrate preparations of cats and in cats anaesthetized with chloralose during the start of inhalation of volatile anaesthetic agents. Ether, halothane and methoxyflurane all produced these effects when they were placed in contact with the larynx. The responses to ether occurred more rapidly than those to halothane, which in turn had a faster effect than methoxyflurane. In the concentrations used, ether vapour (10–20 per cent) and halothane vapour (6–8 per cent) stimulated laryngospasm and apnoea when administered through either the nasopharynx and larynx, the mid-cervical trachea or the distal trachea and lungs. Methoxyflurane (2.9 per cent) did not have these actions in the trachea and lungs. The responses obtained were detected in the absence of the continuity of the olfactory pathway, due to decerebration in which no loss of trigeminal afferents was occasioned. The importance of nasal, laryngeal, pharyngeal, tracheal and pulmonary stimulation in the production of laryngospasm and apnoea caused by inhaling anaesthetic vapours has been demonstrated.

It has been established that the inhalation by man of irritants may cause depression, slowing and arrest of thoracic respiration (Allen, 1929). The effects differ according to the intensity of the stimulation, and mild irritants may only reduce the inspiratory phase so that the effect is apparent as a change in respiratory rate. The reactions to the inhalation of irritants do not depend on smell since they have been demonstrated in an anosmic patient.

Laryngospasm has been stimulated experimentally by a number of workers (see Rex, 1970) and in particular in studies in the cat (Harrison and Vanik, 1963) in which an analysis was made of the effects of atropine on the course of laryngospasm.

The object of the work described in this paper was to define the sites of stimulation of the upper respiratory tract which may contribute to the occurrence of laryngospasm. The potency of different anaesthetic agents in this regard has been investigated.

METHODS

Preparations.

Sixty-four cats were used; of these fifty-eight were studied as decerebrate preparations, and the rest under chloralose anaesthesia. The animals used were clinically healthy and had not been submitted to anaesthesia for a period of at least a month before they were used in an experiment. Anaesthesia was induced with halothane and maintained during decerebration with ether or the continued administration of halothane. When chloralose (65 mg/kg) was used, it was injected during halothane anaesthesia through a polyethylene tube inserted via the saphenous vein so that its tip lay in the caudal vena cava. Decerebration was at the intercollicular level, the transection being made so as to leave the pons and all the central nervous system caudal to it in continuity. An extensive open dorsal craniotomy technique of decerebration was used after the style of that used by Comline and Titchen (1951) in calves. Experiments of up to 9 hours duration were carried out with consistently reproducible results.

Recording.

Activity of the diaphragm and laryngeal muscles was followed electromyographically with

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the aid of concentric needle electrodes (Adrian and Bronk, 1929) inserted into these muscles. Conventional electromyograms (Basmajian, 1962) were obtained by photographing the display on an oscilloscope. A record of the oscillations in the Y axis of stationary beams was obtained by using a camera in which the film moved past the beams at a constant speed to provide a record with an X axis. A 0.2 sec time marker was provided from a synchronous motor, on the shaft of which was mounted a perforated disc which revolved in front of a light source.

Experimental Manipulations.

(a) Inhalation of volatile anaesthetic agents by face mask with the respiratory tract intact.

In eleven experiments volatile anaesthetic vapours in oxygen were administered through a conical latex rubber mask (Hall, 1957). Eight of the cats were decerebrate preparations, the other three received chloralose (65 mg/kg) intravenously. Ether was administered from a Boyle (BOC) ether vaporizer with the lever in the full-on position and the plunger up. The concentration of ether vapour obtained from the vaporizer in these conditions was between 10 and 20 per cent (Macintosh, Mushin and Epstein, 1963). Halothane was administered from a modified trichloroethylene vaporizer (Hillard, 1957), in a concentration estimated from the calibration curve (British Oxygen Co.) to be 6–8 per cent.

(b) Spraying the pharynx and anterior larynx with volatile anaesthetic agents.

Volatile anaesthetic agents were sprayed from a simple nebulizer on to the pharynx and anterior larynx. During the procedure, the cats were in dorsal recumbency and a gag was used to hold their mouths open. Needle electrodes were placed in the cricothyroid muscle and the diaphragm in fifteen of the experiments, and in three experiments electrodes were placed in the dorsal and lateral cricoarytenoid muscles. An ether spray was used in all the experiments. The effects of ether were compared with halothane in five experiments, and with saline in another four experiments in different preparations. In a series of experiments in the one preparation, the effects of ether were compared with those of saline and halothane. In the first experiments in which ether was sprayed on to the pharynx and larynx, the spray was continued for 30 sec but later the time for which ether was applied was reduced.

(c) Passage of volatile anaesthetic agents into isolated areas of the respiratory tract.

In forty-one decerebrate preparations and one cat under chloralose anaesthesia, anaesthetic vapour and oxygen was passed by mask through the isolated nasopharynx and larynx or through a cannula into the trachea and lungs. The larynx and nasopharynx were isolated by inserting a glass cannula into the cranial end of the divided trachea.

In two cats a segment of trachea with its nerve and blood supply intact was isolated by inserting two cannulae into the trachea (Rex, 1967). Both pointed towards the lungs. The more cranial of these cannulae served to isolate the larynx and nasopharynx from the trachea. The more caudal cannula served to maintain a free airway to the caudal segment of the trachea and the lungs. There was thus a region of the trachea isolated from the larynx cranially and the rest of the trachea and the lungs caudally. In these two preparations anaesthetic vapour could be passed either through the nasopharynx and larynx only, or through the isolated tracheal segment, or into the caudal trachea and lungs. The effects of ether vapour alone were studied in twenty-four experiments, in fifteen the effects of ether and halothane were compared, and in three cats the effects of halothane and methoxyflurane were compared.

RESULTS

In all the experiments, records of the resting activity of the muscles were obtained. These established that in decerebrate and chloralose preparations conditions comparable in at least some respects to normal quiet respiration of the conscious animal were approached.

(a) Inhalation of volatile anaesthetic agents by face mask with the respiratory tract intact.

The administration of ether and halothane or methoxyflurane vapour via a face mask to decerebrate preparations or cats anaesthetized with chloralose produced laryngospasm. Figure 1 shows this phenomenon as it involves the cricothyroid muscle and the diaphragm. Figure 1a shows the activity of the cricothyroid muscle and
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Decerebrate cats. Decerebration under halothane/ether anaesthesia. Electromyographic records of the activity of the cricothyroid muscle (i) and the diaphragm (ii). (Spikes retouched.)

(a) Quiet respiration, breathing oxygen through the mask.
(b) Same preparation as in (a). Shows continuous activity of high frequency of the cricothyroid muscle involving large numbers of motor units (laryngospasm) and apnoea (cessation of diaphragm contraction) when 10-20 per cent ether was inhaled by mask.
(c) Different preparation. Shows continuous cricothyroid activity and apnoea at the end of 48 sec inhalation of halothane by mask. The first action potentials which mark the termination of apnoea can be seen towards the end of the electromyogram recorded from the diaphragm. The start of action potentials from the diaphragm after apnoea may be seen at the end of the trace.

Decerebrate cat. Decerebration under halothane/ether anaesthesia. Electromyographic record of the activity of the lateral cricoarytenoid muscle (an adductor) (i) and dorsal cricoarytenoid muscle (an abductor) (ii). (Spikes retouched.)

(a) Shows the activity in these muscles during quiet respiration. The adductor was active in expiration, the abductor in inspiration.
(b) Shows the marked increase in activity recorded from the lateral cricoarytenoid within 3 sec of spraying the larynx and pharynx with ether (the start of which is indicated by the arrow).

In the same cat, when halothane was sprayed on to the pharynx and anterior larynx in a similar manner 30 minutes later laryngospasm was evident as increased activity of the lateral cricoarytenoid muscle. When rhythmic respiration returned, a prolonged discharge from the dorsal cricoarytenoid was detected, being over twice the duration observed during quiet respiration. The responses described in this preparation are
representative of those obtained in the other preparations studied. The increased activity of the dorsal cricoarytenoid muscle, an abductor, after the spasm of the adductors caused by ether and halothane sprays may be interpreted as a compensatory mechanism leading to an increased diameter of the airway; it should be noted that it was detected towards the end of the application of anaesthetic spray.

(c) Passage of volatile anaesthetic agents into isolated areas of the respiratory tract.

Different effects were stimulated according to the agents which were used. When 10–20 per cent ether was administered by mask through the isolated nasopharynx and larynx, laryngospasm occurred in some experiments within 0.2 sec of the start of administration of the ether. The latency between the start of administration of halothane and methoxyflurane and the occurrence of laryngospasm was longer than it had been with ether. With halothane this latent period varied from 0.6 to 4.0 sec, compared with 0.2 to 2.4 sec for ether and 0.6 to 8.0 sec for methoxyflurane. In decerebrate preparations laryngospasm was stimulated by passing anaesthetic vapours through the nasopharynx and larynx. Olfactory pathways were not involved; these are interrupted by decerebration. The possibility that nasal trigeminal receptors are involved is discussed more fully in a later paper.

Ether and halothane administered directly into the distal trachea and lungs caused laryngospasm and an interruption of the regular rhythmic contractions of the diaphragm. Methoxyflurane, however, had no effect, when administered directly into the trachea, although when given by face mask it had stimulated laryngospasm and apnoea. The differences in the effects of 6–8 per cent halothane and of 2.9 per cent methoxyflurane when administered into the distal trachea are shown in figures 4a and 4b. Figure 4c illustrates the laryngospasm and apnoea which was produced in the same animals with the same concentration of methoxyflurane, but administered via a face mask to stimulate the nasopharynx and larynx.

Although the effects of stimulation of the respiratory tract by ether, halothane and methoxyflurane were investigated, the main part of the work was concerned with the effects of ether. In two experiments, a segment of trachea, with its nerve and blood supply intact, was isolated by
inserting a second cannula into the distal part of the transected trachea. The passage of ether vapour through this isolated segment of trachea stimulated laryngospasm and apnoea. Thus it was demonstrated that laryngospasm and apnoea or abnormal diaphragmatic activity may be stimulated by the exposure of the trachea alone, and of the trachea and lungs, as well as the larynx, to sudden high concentrations of halothane and ether. Methoxyflurane appeared to have its effects, in the concentrations used, only on the nasopharynx and larynx.

![Diagram](image)

**Fig. 4**

Decerebrate cat. Decerebration under halothane/ether anaesthesia. Time marker 0.2 sec (interruptions of the time trace and arrows indicate the start of administration of the anaesthetic agents). Electromyographic records of the activity of the cricothyroid muscle (i) and the diaphragm (ii). (Spikes retouched.)

(a) Shows laryngospasm and an interruption of the regular diaphragmatic rhythm when 6-8 per cent halothane was administered into a tracheal cannula and thus trachea and lungs exposed to the anaesthetic vapour.

(b) Shows that neither laryngospasm nor any change in respiratory rhythm occurred when 2.9 per cent methoxyflurane was administered through a tracheal cannula, which contrasts with

(c) which shows that the administration of 2.9 per cent methoxyflurane by mask through the nasopharynx and larynx stimulated laryngospasm and apnoea.

**DISCUSSION**

Widdicombe (1964) has drawn attention to the possibility of there being pain endings and cold receptors as well as chemoreceptors in the larynx. In the experiments reported in section (b) of this paper, spraying ether or halothane on the larynx and pharynx stimulated greater discharges from the cricothyroid muscles than those produced by 0.9 per cent saline at 37°C and 26°C. This could be interpreted as being due to cooling of the mucosa when ether and halothane droplets vaporized, but the fact that in later experiments discharges of similar magnitude were stimulated by ether and halothane vapour makes this unlikely. Although spraying with saline at 5°C was not attempted in this study, it is clear from the work of Dirnhuber, Green and Tregear (1965) that receptors in the cat’s larynx stimulated by irritant chemicals exhibited cold-sensitivity and may be stimulated at temperatures as widely apart as 5°C and 32°C.

An important aspect of these experiments was the demonstration of compensatory activity of the dorsal cricoarytenoid muscle after laryngospasm, seen as prolonged activity of this muscle during the inspiratory phase of the cycle after laryngospasm. How this arises has not been studied; it would be of interest to examine the activity of this muscle in the early stages of anoxia and hypercapnia.

It is interesting that there should be differences in the latencies between the application of ether, halothane and methoxyflurane and their effects. This may be in part due to different relative concentrations of these agents as well as to differences in the solubility in blood of the different agents. Diethyl ether is more soluble in blood than halothane or methoxyflurane and was most rapid in its effects; it is less soluble in lipids than halothane or methoxyflurane. In this connexion it should be noted that Paintal (1957) found that the latencies between the start of insufflation and the onset of a discharge from pulmonary deflation receptors were longer after trichloroethylene than after ether. Ether is more soluble in blood than trichloroethylene. Variations in latency must also depend on the condition of the mucous membrane surface, presence of secretions, blood supply and similar factors.

Also of interest is the failure of methoxyflurane, administered through a tracheal cannula to the distal trachea and lungs, to stimulate laryngospasm or changes in the respiratory rhythm, although it had done so when administered by mask. Halothane did stimulate the laryngeal reflex when administered by tracheal cannula. Amongst possible explanations was that absorption of methoxyflurane was too slow, because the threshold of the receptors was not reached, or because
those receptors sensitive to ether and halothane are not sensitive to methoxyflurane.

The discharge stimulated from the cricothyroid muscle when ether vapour was passed through an isolated tracheal segment was less intense and of shorter duration than when it was administered by mask to the nasopharynx and larynx, or by cannula to the distal trachea and lungs. This would represent a very small region of the respiratory tract being stimulated. However, Elftman’s observation (1943) on the relative paucity of nerve endings in the trachea compared with other parts of the respiratory tract may have some bearing. She stated that there were more afferent endings in the region of the tracheal bifurcation and the lung hilus, but added the reservation that the amount of muscle was greater in these regions. Dixon and Brodie (1903) noted that sensitivity of the mucous membrane to chemical irritants became less farther down the respiratory tract: Widdicombe (1954) has also commented on differences in sensitivity of different regions of the respiratory tract.

Conroe (1965) discussed the possibility of there being chemoreceptors in the lung bed, and the present findings can be interpreted as having involved stimulation of pulmonary chemoreceptors as well as those in the trachea and larynx. However, the possibility must be considered that the anaesthetic agents serve to sensitize receptors which are not characteristically chemoreceptors. Paintal (1957) found that pulmonary deflation receptors were stimulated and sensitized by ether, trichloroethylene or chloroform. The initial increase in excitability was followed by a depression or total loss of excitability of the receptors involved. These are important features of the action of anaesthetic agents.

It was not possible to establish a concentration at which ether and halothane were at a threshold for the stimulation of laryngospasm which was applicable to every preparation. It remains of interest to do so since one possibility of avoiding laryngospasm in the administration of volatile agents is to give them at less than the threshold concentration for stimulation of the reflex.

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LA PRODUCTION DU LARYNGOSPASME CHEZ LE CHAT PAR DES AGENTS ANESTHESIQUES VOLATILES

SOMMAIRE

Du laryngospasme et de l'apnée ou des altérations du rythme de la respiration ont été produites dans des préparations décérébrées de chats et chez des chats anesthésiés au chloralose durant le début de l'inhalation d'agents anesthésiques volatiles. L'éther, l'halothane et le methoxyflurane ont tous produit ces effets, lorsqu'ils étaient mis en contact avec le larynx. Les réactions à l'éther furent plus rapides que celles à l'halothane, qui à son tour agit plus rapidement que le methoxyflurane. La vapeur d'éther (10-20 pourcent) et la vapeur d'halothane (6-8 pourcent) ont aux concentrations utilisées stimulé le laryngospasme et l'apnée, lorsqu'elles furent administrées soit par le nasopharynx et larynx, la trachée mi-cervicale ou la trachée distale et les poumons. Les réactions obtenues furent détectées en absence de la continuité des voies olfactrices, due à la décérébration sans perte des fibres afférentes trigémérales. L'importance de la stimulation nasale, laryngé, pharyngé, trachéale et pulmonaire dans la production du laryngospasme et de l'apnée, causées par l'inhalation de vapeurs anesthésiques, a été démontrée.

NORTH OF ENGLAND SOCIETY OF ANAESTHETISTS

Programme 1970–71

1970
FRIDAY, NOVEMBER 13. Dr J. E. Utting, Department of Anaesthesia, University of Liverpool: “Dreaming and Awareness during Anaesthesia”.
FRIDAY, DECEMBER 11. Dr L. J. Dunkin and Dr C. W. Thomson, Regional Neurosurgical Centre, Newcastle General Hospital: “Head Injuries”.

1971
FRIDAY, APRIL 23. Dr W. D. Wylie, Department of Anaesthetics, St Thomas’s Hospital, London: “Some Medico-Legal Aspects of Anaesthesia”.
FRIDAY, MAY 14. MEMBERS’ NIGHT. This meeting will consist of short papers by some members of the Society and will commence at 6.30 p.m. This will be followed by a Buffet Supper in the Medical Staff Common Room of the Royal Victoria Infirmary at 8 p.m. for 8.30 p.m. for members and wives.

There will not be an ordinary meeting of the Society in March but arrangements are in hand with the University Department of Anaesthesia for a one-day Symposium on “Anaesthesia and Obstetrics” on Saturday, March 20.

Meetings are held in The New Lecture Theatre, R.V.I., Newcastle upon Tyne, at 8 p.m. Buffet suppers will be held as previously in the board room from 6.30 p.m. and coffee will be available in the ante-room to the lecture theatre from 7.30 p.m. onwards.

Honorary Secretary: Dr D. T. Pearson, c/o DEPARTMENT OF ANAESTHESIA, ROYAL VICTORIA INFIRMARY, NEWCASTLE UPON TYNE, NE1 4LP.