CONVULSIVE PHENOMENA IN HYPERTHERMIC DOGS DURING ANESTHESIA

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THE serious consequences of "ether convulsions" have stimulated interest and investigative activity especially after the occurrence of a flurry of episodes as reported in 1927 by Wilson[1] and Pinson.[2] Emphasis has been directed toward the delineation of causative factors; many of those which have been suggested as contributory have been listed by Lundy.[3]

Recent studies by Owens *et al.*[4, 5, 6] have led to the contention that cellular damage in the brain precedes "ether convulsions." They inferred that the antecedent of this damage was embolization of fat. Their supporting evidence was the finding of fat emboli in the brain, degeneration of cerebellar Purkinje cells, behavioral changes, and ataxia in dogs subsequent to their survival of a convulsive episode during ether anesthesia and hyperthermia. Prognostically they asserted[5] that "control of the gross seizures under such circumstances by the use of barbiturates as commonly practiced by anesthesiologists may be desirable but in all probability is a rather futile and symptomatic therapeutic gesture since the convulsive movements merely reflect the underlying cellular damage to the brain."

The purpose of this investigation was twofold: (1) to evaluate the concept of fat embolization as the basic mechanism responsible for "ether convulsions" and challenge that regarding the futility of active therapy, and (2) to include a study of the convulsive tendencies of some of the newer anesthetics in hyperthermic dogs.

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PROCEDURE

The anesthetic agents studied were: ethyl ether, vinyl ether (Vinethene), ethyl vinyl ether (Vinamar), trifluoroethyl vinyl ether (Fluoromar)*, halothane (Fluothane)*, fluether (azeotropic mixture of halothane and ethyl ether). The fluether was prepared by mixing two volumes of halothane with one volume of ethyl ether and collecting the distillate boiling at 51 C. to 52 C.

Unmedicated, mongrel dogs weighing 6 to 14 kg. were fasted from food but not from water for 24 hours preceding experiments. Needle electrodes were inserted into the scalp over the right and left temporal areas and into the right ear for recording electroencephalographic tracings. Electrocardiograms were obtained from standard lead 1, using similar electrodes. Both types of tracings were recorded continuously. Rectal temperature was monitored continually.

A Foregger double kettle anesthetic machine was employed for the administration of all anesthetic agents with oxygen. Induction of anesthesia was accomplished using a face mask and a to-and-fro system with flow rates of oxygen of 5 to 6 liters per minute. After endotracheal intubation, a circle absorption system was employed with constant manual assistance of respiration. A polyethylene catheter was inserted through the endotracheal tube into the tracheobronchial tree for the purpose of sampling end-expiratory gases. The carbon dioxide concentration of these gases was determined intermittently using a Beckman infrared gas analyzer; permanent tracings of this parameter were recorded on an Offner dynograph.

Hyperthermia was induced by immersing the animal in a bath of water of 45 C. maximum temperature. Protocol was established

* Fluothane was supplied by Ayerst Laboratories Inc., and Vinamar and Fluoromar by Ohio Chemical & Surgical Equipment Co.

TABLE 1

FREQUENCY OF OBSERVED CONVULSIVE PHENOMENA

	Overt Convulsions	EEG Seizures Only	No Abnormalities
Vinyl Ether	5	0	0
Ethyl Vinyl Ether	5	0	0
Ethyl Ether	5	0	0
Trifluoroethyl Vinyl Ether	2	1	2
Fluether	0	1	4
Halothane	0	1	4

to maintain rectal temperature between 40.6 C. and 42.2 C. for a period of one hour before discontinuing anesthesia and cooling. If during the procedure an electroencephalographic paroxysmal discharge or overt convulsion occurred, administration of the anesthetic agent was discontinued and body temperature reduced by immersion of the animal in cold water. Oxygen administration was continued until body temperature had returned to control level.

At the conclusion of the procedure the animal was returned to its cage and maintained on a normal diet for two weeks during which time it was periodically observed for evidence of neurological deficits. At the end of this period the dog was sacrificed by intravenous injection of potassium chloride and the brain removed. After ten days of fixation in 10 per cent formalin, samples from both parietal lobes, basal ganglia and cerebellum were obtained for histologic study. Duplicate specimens were prepared from each sample. One specimen was stained with hematoxylin and eosin; the other was frozen and stained for fat with the oil red O technique. All histologic specimens were examined for evidence of fat emboli and cellular degeneration by a pathologist (F.A.) who was unaware of the treatments of the animals from which they were obtained.

Five dogs were studied with each of the anesthetic agents. Five other animals not subjected to anesthesia or hyperthermia were subjected to the same housing conditions and diet for a period of two weeks, then sacrificed to obtain their brains for comparative observations.

RESULTS

Table 1 lists the frequencies of occurrence of overt convulsions and electroencephalographic paroxysmal discharges (EEG seizures) with each anesthetic agent.

Figure 1 illustrates a typical EEG seizure for each agent.

Figure 2 is a graphic representation on a thermo-temporal basis of the data in table 1. Each symbol characterizes a single animal. Solid symbols represent simultaneous occurrences of EEG seizures and overt convulsions. Dotted symbols indicate EEG seizures in the absence of overt convulsions. Hollow symbols with arrows indicate the absence of convulsive phenomena throughout the duration of the experiment. The location of each symbol with reference to the ordinate indicates the temperature at which convulsive phenomena occurred or the highest temperature reached during the one hour of maintenance above 40.6 C. in instances when no abnormal behavior was noted. Location of the symbols with reference to the abscissa represent duration of anesthesia. The reflections of the dotted lines upon the horizontal one, indicate spans of time between achievement of a temperature elevation to 40.6 C. and the onset of convulsive phenomena.

Two dogs died during the course of the experiments. One of these expired while convulsing during anesthesia with ethyl ether

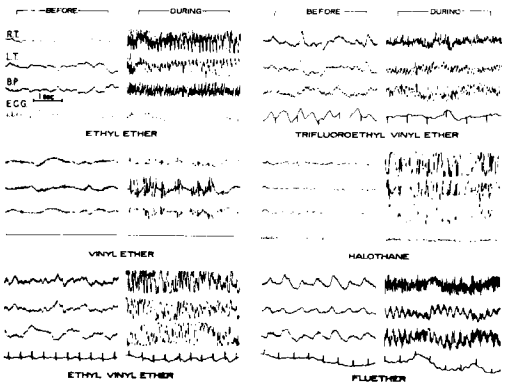

FIG. 1. Typical electroencephalographic paroxysmal patterns for individual anesthetic agents. The "before" tracings were recorded several minutes prior to the onset of seizures. R.T., right temporal, monopolar; L.T., left temporal, monopolar; B.P., bipolar, right to left temporal.

at a body temperature of 42.0 C. Reduction of body temperature in this instance was slow and the cause of death was apparently heart failure. The other animal, after reaching a body temperature of 40.6 C. during anesthesia with trifluoroethyl vinyl ether, developed intermittent ventricular arrhythmias but survived until the end of the experiment without convulsive phenomena. The highest body temperature achieved in this animal was 40.9 C. shortly before expiration from ventricular fibrillation.

Neurological deficits were not apparent in any of the animals during the postanesthetic period of observation. One each of the groups of animals which had received ethyl ether, trifluoroethyl vinyl ether and vinyl ether expired on the sixth, second and fifth postanesthetic days respectively. Recovery from anesthesia had been uneventful in all three instances. The animal which had received trifluoroethyl vinyl ether had not experienced convulsive phenomena during the experiment.

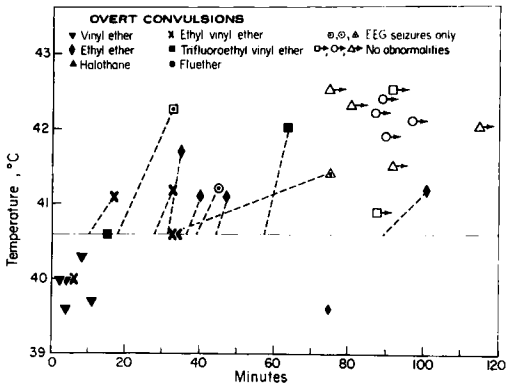

FIG. 2. Thermo-temporal representation of convulsive phenomena in individual animals. Ordinate is temperature of occurrence of convulsive phenomena or highest level reached during one hour period of maintenance above 40.6 C. in instances when no abnormalities were noted. Abscissa is duration of anesthesia in minutes. Reflections of dotted lines upon the horizontal one at 40.6 C. represent the duration of maintenance at or above that temperature prior to convulsive phenomena.

Histologic examination of all stained specimens revealed occasional, small fat emboli within cerebral vessels of only four of the animals. Ethyl ether was implicated twice, halothane once and vinyl ether once. One of the two dogs which had received ethyl ether was the one which expired during the experiment. Fat emboli were not detected in brain sections of any of the three animals which expired during the two week postanesthetic period of observation. The dog which had received halothane and in which fat emboli were observed had not convulsed; neither was it the single animal in that group which had had an EEG seizure during the period of hyperthermic anesthesia.

Carbon dioxide concentrations in the end-expiratory gases did not exceed control levels at the time of convulsions nor at any other time when tested during the experiments. The control levels, determined immediately after tracheal intubation of the animals and prior to hyperthermia, ranged between 3 and 5 per cent.

DISCUSSION

Histolgic findings of our study fail to support the contention of a causal relationship between fat embolization in the brain and "ether convulsions." A few, scattered fat emboli were found in brain specimens of only 2 of the 5 dogs which had convulsed during anesthesia with ethyl ether at elevated body temperatures. Degeneration or absence of cerebellar Purkinje cells were not demonstrable in brain specimens from any of the animals. It should be emphasized that hypoxia and hypercarbia were avoided during the anesthetic periods and that active measures were taken to terminate anesthesia and hyperthermia with the onset of convulsive phenomena. This protocol was established to minimize the confounding of causal with coincidental factors. We do not deny that fat embolization and severe cellular damage may occur during prolonged convulsive episodes at elevated body temperatures. Hypoxia with subsequent cellular degeneration of the brain might be expected if treatment of hyperthermic convulsions were limited to administration of depressant, anti-convulsant drugs. The benefits of prompt, active therapy—discontinuation of anesthetic administration, adequate ventilation with oxygen and reduction of body temperature—were demonstrated by the absence of behavioral changes, ataxia and degeneration of cerebellar Purkinje cells.

The seriousness of the possible neurologic sequelae from ether convulsions is indisputable. Our study indicates, however, that these are not inevitable, and hence treatment not futile, if convulsions are terminated shortly after their onset by adequate therapy. The futility of treatment would seem to be attributable to its inadequacy rather than to inevitable fate.

In support on their observations of fat embolization in the brain, Owens and Scott[6] mentioned the studies of Lehman and Moore[7] in 1927. These latter investigators purported to demonstrate fat embolization in the lungs of dogs after ether anesthesia and offered as an explanation the precipiation of previously dissolved lipid when the concentration of the fat solvent (ether) was reduced. It seems reasonable to assume that if the same mechanism of fat embolization applied to the brain, ether convulsions should occur upon emergence from, rather than during sustained surgical anesthesia as they characteristically do. Aside from this temporal inconsistency, recent studies by Cole and associates[8] and Davies and Peltier[9] cast further doubt upon the presumed relationship between fat embolization and ether anesthesia.

Among the anesthetic agents included in our study, ethyl ether was not unique in possessing a convulsive tendency when administered to hyperthermic dogs. From the thermo-temporal data in figure 2, it is evident that the anesthetic agents tested differ in their relative potentialities in this regard. Among the ethers, trifluoroethyl vinyl ether exhibited the least convulsant potentiality. In contrast with the ethers, halothane and its azeotropic mixture with ethyl ether were less convulsant.

Summary

This laboratory study involved a challenge of the concepts: (1) that the basic cause of ether convulsions is fat embolization in the brain and (2) that treatment of ether convulsions is probably futile. It also concerned an investigation in hyperthermic dogs of the convulsive potentialities of a series of volatile anesthetic agents including: ethyl ether, vinyl ether, ethyl vinyl ether, trifluoroethyl vinyl ether, halothane and fluether.

Our observations neither support the concept of cerebral embolization by fat as the cause of convulsions with ether or any other agent tested, nor the opinion regarding the futility of therapy directed toward the termination of convulsions. A positive plan has been suggested for effective treatment of convulsions occurring during anesthesia and hyperthermia.

The anesthetics studied exhibited an interesting array of convulsive activity ranging from vinyl ether with the highest tendency on a thermo-temporal basis to halothane at the other extreme. This latter observation suggests that among these drugs, halothane may have a selective role in the anesthetization of febrile patients.

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