OBSERVATIONS ON CYCLOPENTANE AS AN ANESTHETIC AGENT *

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CYCLOPROPANE has been in use as an anesthetic agent for about fifteen years. Recently cyclobutane has been reported (1) to have properties which would make possible its use as an anesthetic agent, although its scarcity would seem to prohibit widespread use unless a new and inexpensive method of preparation is found. Cyclopentane was employed by Lazarew (2) in a few experiments in which he observed that a concentration sufficient to produce anesthesia also caused respiratory arrest. The purity of his cyclopentane was not stated. Cyclohexane has been reported (3, 4) to have properties which would prohibit its use in anesthesia. Cyclopropane (5) and cyclobutane (6) both exhibit the property of sensitization of the automatic tissue of the heart to epinephrine. During the past few years a method has been devised for separating cyclopentane from petroleum in a very pure state. Because this product is available, pure, and volatile, it seemed worth while to investigate its properties as a possible anesthetic agent and to determine its effect on cardiac tissue.

METHODS

Investigations were carried out using mice as subjects in a test jar by essentially the method of Henderson and Johnston (4). Their method was modified in that instead of a heating plate, provision was made for evaporation of measured quantities of liquid anesthetic agents by dropping them onto the concave bottom of an inverted 1-ounce bottle which was warmed by water circulating through glass tubing inserted through the stopper of the large test jar. The liquid was introduced onto the concave surface through a needle passed through the rubber stopper of the jar. Another needle was put through the rubber stopper about 1 cm. distant from the first needle. To this was attached an empty 5 cc. syringe and movements of its plunger aided greatly in evaporating the fluid from the warm surface below. A rubber balloon outside the jar was connected to the atmosphere in the jar by a glass tube through the stopper to provide for expansion of the gaseous contents of the jar as the anesthetic liquid evaporated. Soda lime, used

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to absorb carbon dioxide, was put on the bottom of the test jar beneath a wire mesh which supported the mice. A water manometer was employed, and provision was made for keeping the manometer level constant by introducing oxygen as fast as the mice used it.

Young adult Swiss mice were used, each weighing between 17 and 22 Gm. The anesthetic index (concentration of agent for respiratory arrest divided by concentration for surgical anesthesia) was determined on individual mice. The starting concentration of the anesthetic agent in air was about 2 per cent less than that found in preliminary tests to be required to cause sleep within ten minutes. The concentration was then increased 1 per cent each five minutes. Surgical anesthesia was established by loss of response to mechanical stimulation, and the concentrations at which this occurred and at which respiratory arrest ensued were recorded. The anesthetic indexes of ether, cyclopentane and cyclohexane were determined.

Another set of data was obtained with mice to find the proportion of the group which survived exposure to known concentrations of cyclopentane or cyclohexane during a ten minute period of anesthesia. Induction and recovery times were noted. Recovery was taken as the point at which the mice would turn onto all four legs and walk or run.

Dogs were used to obtain information regarding the ability of cyclopentane to sensitize automatic cardiac tissue to epinephrine. The technic of Meek, Hathaway, and Orth (5) was employed. This entailed injecting intravenously 0.01 mg. per kilogram of epinephrine over a period of fifty seconds. The Sanborn Viso-Cardiette was used to record cardiac action. It has been reported that dibenamine (7) protects cardiac tissue against arrhythmias caused by epinephrine using cyclopropane anesthesia. To learn whether dibenamine gave similar protection under cyclopentane anesthesia, 5 dogs were given 20 mg. per kilogram of dibenamine intravenously over a period of fifteen minutes. After at least two hours had elapsed the animals were anesthetized with cyclopentane and epinephrine was injected.

The National Bureau of Standards reported that, by freezing point determinations, the cyclopentane was 99.95 per cent pure. The most probable impurity was 2,2-dimethylbutane. The cyclohexane was 95 per cent pure by infra-red analysis, and the other 5 per cent consisted of six- and seven-carbon paraffins and seven-carbon naphthenes and methylcyclopentane. The ether was USP anesthetic ether.

RESULTS

The anesthetic index found for ether on 33 mice was 2.07; sigma 0.27. For cyclopentane on 65 mice the anesthetic index was 1.56; sigma 0.26. With 34 mice the anesthetic index for cyclohexane was 1.82; sigma 0.18.

Table 1 presents the data on the effects of various concentrations of the anesthetic agents. Most mice went to sleep with about 8 per cent cyclopentane and encountered respiratory arrest with about 12 per cent.

With cyclohexane the corresponding values were 3 and 6 per cent. It will be seen that induction into and recovery from cyclopentane and cyclohexane anesthesia were rapid. Induction of mice with cyclopentane, especially at the higher concentrations, caused extreme excitement which lasted about thirty seconds. Sleep with cyclopentane was usually quiet and the animals remained flaccid, but in a few cases there were jerks of the hind legs just preceding respiratory arrest. More striking than the relatively low anesthetic index of 1.56 for cyclopentane was the fact that an occasional mouse died at the same con-

TABLE 1

MICE EXPOSED TO CYCLOPENTANE

Cyclopentane, Per Cent	Number of Mice	Number Asleep in 10 Minutes	Number Dead after 10 Minutes Sleep	Average Induction, Seconds	Average Recovery, Seconds
5	11	0	0	—	—
6	30	0	0	—	—
7	66	17	6	470	35
8	45	44	3	180	54
9	49	49	12	133	137
10	50	50	16	85	148
11	30	30	19	94	140
12	30	30	24	90	140
13	30	30	25	97	145
14	30	30	30	91	—
15	15	15	15	90	—

MICE EXPOSED TO CYCLOHEXANE

Cyclohexane, Per Cent	Number of Mice	Number Asleep in 10 Minutes	Number Dead after 10 Minutes Sleep	Average Induction, Seconds	Average Recovery, Seconds
2	38	0	0	—	—
3	43	32	0	315	20
4	41	41	7	150	106
5	30	30	10	130	147
6	48	48	45	107	210
7	30	30	30	106	—

Statistical analysis of values for both cyclopentane and cyclohexane shows P is less than 0.01, indicating that the values are highly significant.

centration which was required to produce surgical anesthesia. Table 1 shows no anesthesia at concentrations of 5 or 6 per cent for ten minutes. Longer exposures to these concentrations did produce anesthesia, but about fifteen minutes was required for induction at 6 per cent concentration.

With cyclohexane the same type of central nervous stimulation was observed as was noted by Lazarew (3) and by Henderson and Johnston (4). At a concentration of 5 per cent or higher, mice underwent clonus for about five seconds, followed by a tetanic spasm characterized

by extension of all four legs which lasted about fifteen seconds and was then followed by death or by reversion to normal quiet breathing and flaccidity. This series of reactions appeared a few minutes after the animal was seemingly sound asleep and relaxed.

Both cyclopentane and cyclohexane caused respiratory arrest before causing cardiac arrest. Hearts of animals removed from the jar after respiratory arrest were observed beating for periods varying from fifteen seconds to 120 seconds with cyclopentane and from fifteen seconds to 270 seconds with cyclohexane. It was difficult, however, after producing respiratory arrest with either agent to resuscitate the mice by artificial respiration.

TABLE 2

EFFECT OF EPINEPHRINE* ON ELECTROCARDIOGRAMS OF DOGS

	Controls Awake	Cyclopropane	Cyclopentane	Cyclohexane	Dibenamine plus Cyclopropane	Dibenamine plus Cyclopentane
Number of Dogs	15	7	14	5	5	5
A-V Block	2	0	3	3	0	0
Nodal Extrasystoles	9	3	7	1	0	0
Ventricular extrasystoles	1	4	2	0	0	0
Nodal Rhythm	2	1	1	1	0	0
Original Tachycardia	0	7	12	5	0	0
Original Bradycardia	13	0	0	0	0	0
Ventricular Fibrillation	0	2	0	0	0	0
Sinus Tachycardia	1	7	12	5	3 (Mild)	5 (Mild)

* 0.01 mg. per kilogram was injected intravenously in fifty seconds.

Experiments with dogs indicated also that cyclopentane and cyclohexane are potent anesthetic agents. More excitement was observed in putting dogs to sleep with cyclopentane than was observed with either ether or cyclohexane. On recovery from cyclopentane anesthesia, dogs were confused for about 5 minutes after their reflexes had returned. Electrocardiograms revealed that both cyclopentane and cyclohexane sensitize the automatic tissue of the heart to epinephrine, although the irregularities with these compounds were less striking than those seen using cyclopropane. Table 2 gives an analysis of electrocardiographic results. Seven dogs anesthetized with cyclopropane gave results quite similar to those reported by Meek et al. (5). Two of the 7 dogs went into ventricular fibrillation and died. Sixteen dogs were anesthetized with cyclopentane, 1 of which died before any epinephrine was injected, indicating that severe reaction to this agent may occur in dogs as well as in mice. The most constant finding with both cyclopentane and cyclohexane after injection of epinephrine was tachycardia which appeared immediately and persisted for approximately one minute.

Electrocardiograms on dogs after injection of dibenamine, followed several hours later by injection of epinephrine under cyclopropane or

cyclopentane anesthesia, showed records completely analogous to those reported originally by Nickerson and Goodman (7) on dibenamine and epinephrine using cyclopropane anesthesia. Specifically, cardiac irregularities were prevented except for a slight sinus tachycardia.

DISCUSSION

Lazarew (2) reported that the anesthetic concentration of cyclopentane was identical with the fatal concentration. The results reported here indicate that the concentration that causes respiratory arrest is on the average 1.56 times that necessary to produce anesthesia. Lazarew observed sleep and death with a concentration only half as great as that which was found necessary for sleep in this investigation, namely, 0.0015 mols per liter (3.4 per cent) as against 0.0035 mols per liter (8 per cent). He used a synthetic product whose purity was not reported. The cyclopentane used in this study was 99.95 per cent pure. Lazarew evidently did not provide for absorption of the exhaled carbon dioxide. These differences could account for the variation of concentration.

Henderson and Johnston (4) were unable to account for the difference in concentration required by mice for sleep using cyclohexane anesthesia as observed by themselves and by Lazarew (3). Lazarew reported a requirement of 0.00059 mols per liter (1.3 per cent) and Henderson and Johnston found a value of 0.00148 mols per liter (3.3 per cent). The value found in this investigation was 0.00134 mols per liter (3 per cent), which agrees reasonably well with Henderson and Johnston's value. Again, Lazarew's material was presumably synthetic and was of unreported purity. The material used in this study was isolated from petroleum, and was 95 per cent pure. It is conceivable that somewhat different observations might be made when material which is more than 95 per cent pure becomes available.

In spite of the potency of cyclopentane, its volatility, its availability, the rapid recovery from its use, and the fact that it may be somewhat less active as a sensitizing agent to epinephrine than is cyclopropane on the automatic tissue of the heart, its use as an anesthetic agent cannot be recommended, because of the pronounced excitement observed during even a rapid induction because of a relatively low anesthetic index and because of an occasional death owing to its activity at a very low concentration. Cyclohexane causes such central nervous effects as to preclude its use as an anesthetic agent.

The concentration of cyclopropane necessary for anesthesia of mice is 0.007 mols per liter (4). Cyclobutane appears to be somewhat more potent (1), but the figures are not yet published. Cyclopentane requires 0.0035 mols per liter, and cyclohexane requires 0.00135 mols per liter. These cyclohydrocarbons would seem, therefore, to act in accord with the generalization that the anesthetic potency increases with increase in molecular weight.

Dibenamine afforded strong protective action for cardiac automatic tissue against irregularities induced by epinephrine while the dogs were anesthetized with either cyclopropane or cyclopentane. The observation with cyclopropane was identical with that using cyclopentane. The tachycardia observed after injection of epinephrine was minor; however, the bradycardia seen after giving epinephrine to the control dogs was not observed after dibenamine.

SUMMARY

The anesthetic index for cyclopentane with mice was 1.56; for cyclohexane it was 1.82; for ether the value was 2.07.

Cyclopentane caused severe excitement during rapid induction of anesthesia in mice and dogs. This was followed by flaccidity during anesthesia.

A few minutes after induction of anesthesia in mice using cyclohexane there was clonus, tonus, and tetanic extensor spasm of the legs. Dogs did not exhibit these phenomena.

Cyclopentane and cyclohexane sensitized the automatic tissue of the heart of the dog to epinephrine to about the same degree.

Dibenamine protected the heart of the dog against the irregularities (other than slight tachycardia) caused by epinephrine using cyclopropane or cyclopentane anesthesia.

Neither cyclopentane nor cyclohexane appears to be safe for use as an anesthetic agent.

ADDENDUM

Since this paper was submitted, cyclohexane of 99.95 per cent purity * has been obtained and used as described above for the 95 per cent cyclohexane. The type of central nervous system reactions, the per cent of cyclohexane required for anesthesia, the per cent mortality, induction and recovery times were not significantly different from those found for the 95 per cent cyclohexane.

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