THE ANESTHETIC PROPERTIES OF CYCLOBUTANE * †

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SOME twenty years have elapsed since the anesthetic properties of cyclopropane first were described (1, 2). In this interval, as a result of many clinical and pharmacologic observations, the advantages and disadvantages of cyclopropane have become apparent. The major advantages of this agent for general anesthesia are the ease of control, the potency, and the rapidity of induction and emergence. In certain situations other favorable attributes may be the depressant effect on respiration which leads to ready control of that function and an effect on the finer peripheral blood vessels, giving rise to compensatory vascular reactions during blood loss or some types of shock (3). On the other hand, cyclopropane is a combustible agent; it may produce characteristic types of cardiac arrhythmias and elevation of the arterial blood pressure, cause respiratory acidosis, and, possibly, provide less muscular relaxation than diethyl ether. For these reasons, cyclopropane remains a controversial drug. A substitute for cyclopropane which retains the favorable and lacks the undesirable qualities would be a valuable addition to the inhalational agents at hand.

As part of a program designed to discover better anesthetic agents, Krantz and co-workers have synthesized and investigated the properties of cyclobutane the next higher homologue of cyclopropane (4, 5). This report presents our observations of the effects of cyclobutane in human beings.§ Preliminary studies by Krantz have been scant owing mainly to the small supply of anesthetic available. Cyclobutane is synthesized by means of an expensive and cumbersome process. This gas is combustible. Its physical characteristics (4) suggest that it should behave like cyclopropane. With a standard test dose of epinephrine, cyclobutane already has been shown to produce multifocal ventricular tachycardia in dogs. Thus, in order to replace cyclopropane, cyclobutane would have to perform far better than its congener. This has

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been the measure by which the suitability of cyclobutane has been judged and found wanting.

CLINICAL MATERIAL AND METHODS

Cyclobutane was used to anesthetize 12 women who were to undergo minor gynecologic operations. The ages and estimated physical status of these patients are listed in table 1. All were in good health, without complicating ailments. Each subject was given morphine sulfate, 8 to 10 mg., and scopolamine hydrobromide, 0.3 to 0.6 mg., by hypodermic injection one hour before anesthesia was begun. Cyclobutane was given by means of a closed circle carbon dioxide absorption system through cyclopropane flowmeters in the same manner in which cyclopropane usually is given in this clinic. Administration was begun with a reservoir bag containing only oxygen, and cyclobutane and oxygen in equal volumes were administered until the surgical stage of anesthesia was reached. Thereafter, the concentration of cyclobutane was decreased and kept at levels suitable for maintenance of anesthesia in the first or second plane. Respiration was assisted or controlled if necessary. The pulse rate and arterial blood pressure (by the auscultatory method) were measured at frequent intervals. In half of the cases, electrocardiograms were made whenever irregularities of the pulse were detected. Measurements of inhaled and hemal concentrations of cyclobutane, oxygen and carbon dioxide were not made during these studies.

OBSERVATIONS

1. *Controllability and Potency.* The times for induction of anesthesia ranged from three to ten minutes (table I). Although cyclobutane seemed not to be irritating to smell, induction was uneventful in only 2 cases. In 6 there was mild to severe excitement and coughing, breath holding, and laryngospasm occurred in others. The onset of the third stage was readily detected by the loss of lid tone, relaxation of the jaw or beginning respiratory depression. The signs of the first plane of the third stage of anesthesia, ocular movements, lacrimation, and pupillary responses, were clearly seen. In 2 cases there was pupillary dilatation when the other signs indicated deep first or second plane anesthesia. Despite relatively long periods of inhalation of cyclobutane, it was impossible in most cases to attain deeper anesthesia even if assisted or controlled respiration were in effect. This suggested a diminished potency in comparison to cyclopropane. Little can be said of the effect on muscular relaxation because the operations were such as not to test relaxation, nor can any definite statement be made about excess bleeding, for the same reason. Emergence from anesthesia was generally uneventful but surprisingly prolonged, extending to seventeen and twenty-three minutes in 2 patients. It cannot be concluded

TABLE 1

CLINICAL OBSERVATIONS DURING CYCLOBUTANE ANESTHESIA

Case	Age	Physical Status	Operation	Preop. Med.	Induction		Emergence	Respiration	Blood Pressure	Pulse	Arrhythmias
					Min.	Remarks					
1 I. H.	60	2	Hyster-ectomy	M.S. 8 mg. Scop.† 0.4 mg.	8	Cough, swallowing, laryngospasm		Poor exchange; apnea 8 min.			During induction electrocardiogram
2 M. B.	46	1	Dilatation and curettage	M.S. 10 mg. Scop. 0.6 mg.	3	Marked excitement	6 min. (op. 27 min.)	Depression 5 min.; obstruction	Elevated	Bradycardia	Pulse 156 and irregular in 11 min.; lasted 8 min.; light plane
3 H. A.	42	1	Dilatation and curettage	M.S. 10 mg. Scop. 0.6 mg.	4	Slight excitement	17 min. (op. 30 min.)	Shallow apnea	Elevated	Slight irregularity preop.	Dropped beats during emergence
4 C. R.	29	1	Breast biopsy	Demerol 75 mg. Scop. 0.4 mg.	3	Swallowing, talking, moving	7 min. (op. 35 min.)	Depressed		Bradycardia	None
5 P. L.	18	1	Dilatation and curettage	M.S. 10 mg. Scop. 0.4 mg.	5	Uneventful	23 min.	Early apnea		Bradycardia before op.	Sudden onset of tachycardia, rate 150, light plane
6 C. M.	50	1	Dilatation and curettage	M.S. 8 mg. Scop. 0.4 mg.	5	Uneventful	9 min.	Early depression, obstruction	Elevated	Bradycardia	Tachycardia 14 min.; rate 160–180; lasted 8 min.; light plane

* Morphine sulfate.
† Scopolamine.

TABLE 1—*Continued*

Case	Age	Physical Status	Operation	Preop. Med.	Induction		Emergence	Respiration	Blood Pressure	Pulse	Arrhythmias
					Min.	Remarks					
7 L. M.	54	1	Dilatation and curettage	M.S. 10 mg. Scop. 0.6 mg.	4	Breath-holding, excitement	Prolonged	Normal	Markedly elevated		Tachycardia during induction; rate 160, then 160–190–200; lasted 10 min.; electrocardiogram
8 R. L.	25	1	Dilatation and curettage	M.S. 10 mg. Scop. 0.5 mg.	10	Poor respiratory exchange	Delayed	Shallow apnea		Bradycardia	Irregular in 14 min.; tachycardia in 27 min.; rate 160–180; electrocardiogram
9 M. H.	43	1	Dilatation and curettage	M.S. 10 mg. Scop. 0.4 mg.	5	Talking, struggling, swallowing, cough, crowing		Depressed	Elevated	Bradycardia	Irregular in 11 min.; 6 min. duration; tachycardia 140–200; sudden reversal
10 S. L.	19	1	Dilatation and curettage	M.S. 8 mg. Scop. 0.3 mg.	3	Wild excitement		Poor exchange		Early tachycardia	Irregular in 5 min., lasted 5 min., in and out; electrocardiogram
11 S. C.	38	1	Dilatation and curettage	M.S. 10 mg. Scop. 0.4 mg.	9	Excitement		Depressed preop.	Elevated		Early irregularity in 2nd stage; electrocardiogram
12 B. T.	36	1	Dilatation and curettage Hysterectomy	M.S. 10 mg. Scop. 0.6 mg.	5	Breath-holding			Elevated	Marked bradycardia	Irregular pulse in 9 min.; dropped beats in induction; electrocardiogram

from these observations that cyclobutane was more or less potent than cyclopropane.

2. *Respiration.* In 9 of the 12 cases there was early and progressive depression of the volume of respiration. This began during induction in one subject, and in 2 others apnea resulted at the end of five and eight minutes, respectively. In all patients it was necessary to assist or control respiration early during anesthesia. Thus, with cyclobutane, the possibility for the development of respiratory acidosis was usually present. The relationship between respiratory acidosis and arterial blood pressure changes during and after anesthesia with cyclopropane has been discussed by Dripps (6). Similar changes, therefore, were expected with cyclobutane.

3. *Circulation.* If there were changes in arterial blood pressure the direction was always toward hypertension. This occurred in 6 individuals in whom both the systolic and diastolic levels were elevated, with a greater elevation of the systolic pressure, similar to the changes usually found with cyclopropane (7). In one case hypertension was marked. In no case did hypotension occur, although neither the depth of anesthesia nor the operation performed would have favored this.

Of all the findings, the most consistent and striking was the appearance of alterations in cardiac rate, rhythm, or both. These were noted in 11 of the 12 patients anesthetized. The changes were detected early in the course of anesthesia and became worrisome if allowed to persist. Bradycardia was observed in 7 individuals as the level of anesthesia deepened, and was often the prelude to a serious arrhythmia. All of the arrhythmias occurred in extremely light planes of anesthesia (appearing from four to fourteen minutes after induction was begun). Within these time intervals, irregularities were detected by palpation of the pulse in 9 indivduals, and tachycardia with ventricular rates ranging from 120 to 240 per minute soon followed. The duration of these arrhythmias was from a few to ten minutes, depending on the measures taken to combat the irregularities. In no case did the arrhythmias disappear quickly in spite of emptying of the anesthetic reservoir bag and repeatedly inflating the lungs with oxygen. Agents such as atropine or procaine amide were not employed to treat the arrhythmias, although theoretically they might have been effective. Changing the anesthetic agent to diethyl ether was easily accomplished and seemed to help terminate cardiac irregularities. A great variety of effects was seen in the electrocardiograms. The usual sequence of changes, however, was the initial appearance of bradycardia followed by displacement of the normal pacemaker, A–V nodal rhythm, ventricular premature contractions, interventricular conduction defects, multifocal ventricular rhythm, and short runs of ventricular tachycardia, more or less in that order. A typical sequence may be seen in figure 1. Some of the tracings were so bizzare as to defy diagnosis. In one subject the arrhythmias could be made to

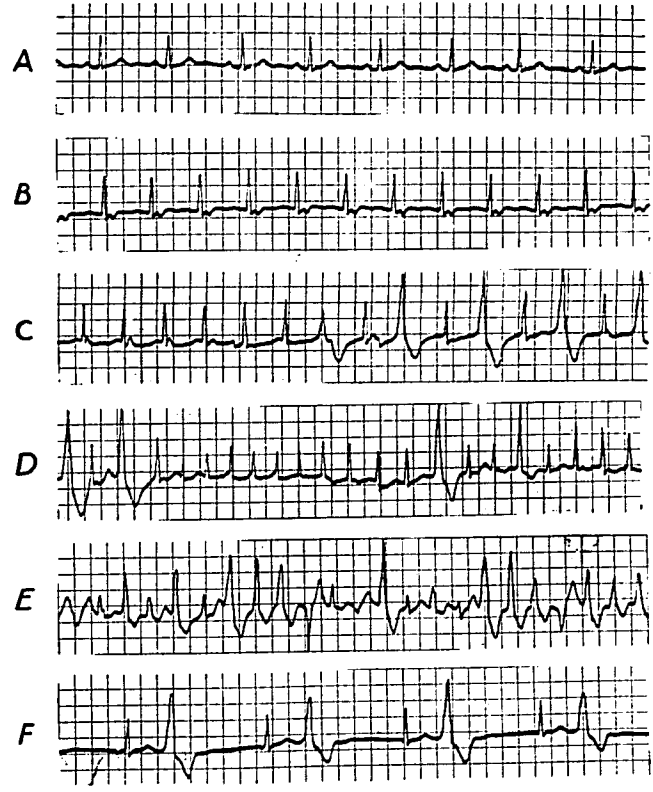

FIG. 1. Selected tracings, in order, from a continuous electrocardiogram—in Case 10, age 19. All tracings are lead 2. A, Normal, before induction of anesthesia with cyclobutane. After induction of anesthesia. B, nodal tachycardia, rate 110. C, Nodal tachycardia of auricular fibrillation, and coupled supraventricular beats with ventricular extrasystoles. D, Run of rapid supraventricular beats, probably auricular fibrillation, rate 220, and ventricular extrasystoles. E. Multifocal ventricular tachycardia, rate 200. F. Supraventricular beats with a wandering pacemaker coupled with ventricular extrasystoles.

appear and disappear at will, depending upon whether more or less cyclobutane were supplied. It was interesting that the blood pressure did not decline during these episodes. In these findings there was then an exact counterpart of the electrocardiographic changes which take place in experimental animals both with cyclopropane and cyclobutane

and of the changes which have been observed during cyclopropane anesthesia in man (8, 9).

DISCUSSION

The foregoing observations indicate that cyclobutane given to human beings mimics the action of cyclopropane in many ways, with some exaggeration of the usual cyclopropane phenomena. However, induction of anesthesia was not rapid, there was question as to potency, and emergence was sometimes prolonged. Reduction of the minute volume of ventilation, arterial hypertension and characteristic cardiac arrhythmias were seen. In administering cyclobutane, the technique followed was that ordinarily used for cyclopropane so that a comparison could be made between the two agents. In so doing, some of the physiologic effects of cyclobutane may have been enhanced. For example, it is known that morphine given for the preoperative medication will increase not only the respiratory depressant qualities of cyclopropane but the vagal effect on the heart as well. If, as the physical properties suggest, cyclobutane is slightly less soluble in blood than cyclopropane, the former is likely to accumulate in the blood more rapidly. If the same inspired tensions of anesthetic were employed for each agent, those effects of cyclobutane which depend on levels of anesthetic attained in the circulating blood might be exaggerated. The respiratory and circulatory changes support this hypothesis. Were these experiments to be repeated without morphine, with a greater quantity of atropine, and with lesser inspired tensions of gas, the characteristics of cyclobutane described by us might have been less evident. Nevertheless, preliminary tests should define those limits beyond which the use of an agent may not be extended.

Whether induction of anesthesia was more rapid with cyclobutane than with cyclopropane cannot be established from these trials. If, as Kety (10) and others have shown, it is the relative solubility in blood of the anesthetic agent which primarily determines the speed of induction of anesthesia, all other factors being equal, one might expect induction to be slightly faster with cyclobutane. The Ostwald solubility coefficient for cyclobutane is 0.138 at 27 C. (4) indicating less solubility than that for cyclopropane with a coefficient of 0.248. It should not be assumed that increasing the rapidity of induction with inhalational agents is an unmixed blessing. If the agent is potent, a rapidly increasing tension in blood may lead to early undesirable respiratory and cardiac effects. Such may be the case with cyclobutane. The potency of cyclobutane seemed to be less than that of cyclopropane, for difficulty was experienced in attaining deeper levels of surgical anesthesia. It is difficult to rationalize this observation other than to state that narcotic potency has not yet been related to any one set of physical characteristics.

The great deterrent to further investigation was the high incidence

of undesirable circulatory changes. A decrease in the minute volume of respiration may have provided the background for the circulatory phenomena seen. Carbon dioxide retention has been linked to the development of hypertension during cyclopropane anesthesia and is sometimes the basic disturbance leading to cardiac arrhythmias (6, 11). It is not the purpose of this paper, however, to discuss further those factors leading to arrhythmias. In 11 of the 12 patients anesthetized with cyclobutane, there were alterations in cardiac rate of rhythm or both. Although the same changes have been seen from time to time during cyclopropane anesthesia, it is doubtful that there would have been an equal number of arrhythmias in a group of normal persons given cyclopropane by those accustomed to using it. The figures most readily available for comparison are those reported by Kurtz, Bennett and Shapiro (9). Of 41 patients anesthetized with cyclopropane, many with heart disease, the incidence of arrhythmias was less than 30 per cent. Multiple focus ventricular tachycardia developed in 4 patients. It was interesting that the arrhythmias developing under cyclobutane arose during light planes of anesthesia. There is disagreement as to the time of appearance of arrhythmias during cyclopropane anesthesia. Some say arrhythmias appear only during deep anesthesia while others maintain that a zone for development of arrhythmias can be by-passed by increasing depth. It is more likely that the tension of anesthetic in circulating blood and auxiliary factors of oxygen lack, carbon dioxide retention, and vagal tone are responsible for the time of appearance of arrhythmias.

SUMMARY AND CONCLUSION

Cyclobutane proved to be an inhalational anesthetic agent which mimics many of the pharmacologic actions of its homologue, cyclopropane. However, induction of anesthesia was usually stormy and not rapid, relative potency was not definitely defined, and emergence was sometimes prolonged. Reduction of respiratory exchange, arterial hypertension, and bradycardia were common occurrences. The outstanding finding was a high incidence of cardiac arrhythmias which were resistant to treatment. Although it is possible that under the conditions of performance of these clinical tests the undesirable characteristics of cyclobutane may have been exaggerated, it seems doubtful that this drug holds much promise as a clinical anesthetic agent.

REFERENCES

1. Henderson, V. E., and Lucas, G. H. W.: Cyclopropane, New Anesthetic, Anesth. & Analg. 9: 1–6 (Jan.–Feb.) 1930.
2. Waters, R. M., and Schmidt, E. R.: Cyclopropane Anesthesia, J.A.M.A. 103: 975–983 (Sept. 29) 1934.
3. Hershey, S. G., and Zweifach, B. W.: Peripheral Vascular Homeostasis in Relation to Anesthetic Agents, Anesthesiology 11: 145–154 (March) 1950.

4. Krantz, J. C.; Carr, C. J.; Vitcha, J. F., and Andersch, M. A.: Anesthetic Properties of Cyclobutane: A Preliminary Report, Anesthesiology 9: 594–600 (Nov.) 1948.
5. Krantz, J. C. *et al.*: Further Study of Anesthesia with Cyclobutane, Anesthesiology 10: 469–472 (July) 1949.
6. Dripps, R. D.: Immediate Decrease of Blood Pressure Seen at Conclusion of Cyclopropane Anesthesia: "Cyclopropane Shock," Anesthesiology 8: 15–35 (Jan.) 1947.
7. Price, H. L.; Conner, E. H., and Dripps, R. D.: Concerning Increase in Central Venous and Arterial Blood Pressures During Cyclopropane Anesthesia in Man, Anesthesiology 14: 1–9 (Jan.) 1953.
8. Meek, W. J.; Hathaway, H. R., and Orth, O. S.: Effects of Ether, Chloroform, and Cyclopropane on Cardiac Automaticity, J. Pharmacol. & Exper. Therap. 61: 240–252 (Nov.) 1937.
9. Kurtz, C. M.; Bennett, J. H., and Shapiro, H. H.: Electrocardiographic Studies During Surgical Anesthesia, J.A.M.A. 106: 434–441 (Feb. 8) 1936.
10. Kety, S. S.: Theory and Applications of Exchange of Inert Gas at Lungs and Tissues, Pharmacol. Rev. 3: 1–41 (March) 1951.
11. Johnstone, Michael: Cyclopropane Anaesthesia and Ventricular Arrhythmias, Brit. Heart J. 12: 239–244 (July) 1950.