PROTECTION BY DIBENAMINE AGAINST "SPONTANEOUS" ARRHYTHMIAS OCCURRING DURING CYCLOPROPANE ANESTHESIA *† ‡

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MANY clinical and experimental reports have confirmed the frequent occurrence of cardiac arrhythmias during the course of cyclopropane anesthesia in laboratory animals and man. Such irregularities often are of a serious nature and include ventricular premature contractions, multifocal ventricular tachycardias and even ventricular fibrillation. A number of anesthetic deaths of patients apparently in good physical condition has been attributed to arrhythmias produced during cyclopropane anesthesia (1). All concentrations of cyclopropane sensitize the myocardium to circulating epinephrine (2), and it is probable that the so-called "spontaneous arrhythmias" occurring in the presence of cyclopropane are the result of the action of endogenous epinephrine or sympathetic nerve activity.

Because of the ability of dibenamine (N,N-dibenzyl-β-chloroethylamine) to block many excitatory effects of epinephrine (3, 4) it was suggested that this drug might provide protection against the cardiac irregularities induced by epinephrine in the presence of cyclopropane. Animal experiments have fully confirmed this expectation (5, 6, 7). Dibenamine and its active congeners were found to be much more effective in this regard than any other agent tested. The present studies were undertaken to determine whether dibenamine would be equally effective in preventing "spontaneous" arrhythmias occurring during cyclopropane anesthesia in man.

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METHODS

The subjects of these experiments were 20 healthy young adults undergoing elective surgery, usually orthopedic procedures, appendectomy or herniorrhaphy. Routine preanesthetic medication consisted of a barbiturate, morphine, and scopolamine. Cyclopropane was the sole anesthetic agent employed and was administered in a closed system with carbon dioxide absorption. Each patient was carried slowly through the planes of surgical anesthesia to respiratory arrest and back to plane 1 or 2 over a period of about thirty minutes. Stages and planes of anesthesia were recorded on the basis of the usual respiratory and reflex signs. In plane 4 and stage IV, adequate oxygenation was maintained by intermittent pressure on the rebreathing bag, except for short periods during which the effects of superimposed hypoxia were studied. Electrocardiographic tracings, usually lead II, were begun several minutes before applying the mask and continued without interruption for at least thirty minutes of anesthesia.

Dibenamine, in the form of a 5 per cent acidified solution of the hydrochloride in propylene glycol and alcohol, ‖ was added to an infusion of about 500 cc. of 5 per cent dextrose or 0.9 per cent sodium chloride solution and administered over a perod of ten to seventy-two minutes (average thirty-eight minutes). Infusion of the vehicle was initiated before addition of the drug, to guard against possible extravasation. The vein was also flushed with 100 cc. of isotonic fluid after completion of the dibenamine infusion. The dibenamine was given seventeen minutes to fourteen hours before operation and in all cases was preceded by administration of 0.1 or 0.2 Gm. of pentobarbital or seconal. Dibenamine has a very persistent action (3, 4, 6) and a nearly maximal effect may be expected to exist from thirty minutes to at least eighteen hours after intravenous administration. Dose ranges of 5.0 to 6.0 mg. per kilogram and 7.0 to 7.5 mg. per kilogram were employed.

Analysis of the electrocardiographic records obtained during the first thirty minutes of each period of anesthesia was undertaken by planes. The length of time each patient was in a given stage or plane of anesthesia was determined and the percentage of that interval occupied by each of four different categories of arrhythmia was ascertained. The classifications recognized were: (1) nodal or auricular rhythm, (2) ventricular beats amounting to less than a third of the total number of beats, (3) ventricular beats amounting to more than a third of the total (including *pulsus bigeminus*), and (4) ventricular tachycardia. These four categories were assigned arbitrary values of 1, 3, 5 and 10, respectively, as a measure of the relative severity of each arrhythmia (table 1). The average severity of the arrhythmias for the entire period in a given plane was then plotted against the depth of anesthesia (fig. 3).

‖ Kindly supplied by Dr. William Gump, Givaudan-Delawanna, Inc., Delawanna, N. J., N,N-dibenzyl-β-chloroethylamine is now being distributed for investigational use by the Smith, Kline and French Laboratories, Philadelphia 1, Pa., under their trade-mark "Dibenamine."

RESULTS

The severity of the arrhythmias encountered in patients who did not receive premedication with dibenamine was found to increase exponentially with the depth of anesthesia (table 1 and fig. 3). Ventricular rhythms were not encountered in stage III, planes 1 and 2, but ventricular complexes appeared in plane 3 and were present in all records obtained during plane 4 and stage IV anesthesia. In plane 4 and particularly in stage IV, periods of ominous multifocal ventricular tachycardia were not uncommon. Figure 1 illustrates three types of ventricular arrhythmias from records taken during plane 4 anesthesia.

Patients treated preoperatively with dibenamine in doses of 5.0 to 6.0 mg. per kilogram, exhibited only a slight reduction in the incidence

TABLE 1

CARDIAC ARRHYTHMIAS EXHIBITED BY PATIENTS IN VARIOUS PLANES AND STAGES OF CYCLOPROPANE ANESTHESIA

Treatment	Depth of Anesthesia	Total Time, minutes	Sinus Rhythm, per cent	Nodal or Auricular Rhythm, per cent	Ventricular Beats <1/3, per cent	Ventricular Beats >1/3, per cent	Ventricular Tachycardia, per cent
Control (7 cases)	III_1	12	96	4	—	—	—
	III_2	31	82	18	—	—	—
	III_3	57	53	34	5	8	—
	III_4	62	50	24	10	13	3
	IV	30	33	24	17	13	13
Dibenamine 5.0 to 6.0 mg. per kilogram (7 cases)	III_1	19	100	—	—	—	—
	III_2	28	96	2	2	—	—
	III_3	57	85	—	4	11	—
	III_4	67	65	9	12	13	1
Dibenamine 7.0 to 7.5 mg. per kilogram (6 cases)	III_1	14	100	—	—	—	—
	III_2	29	95	5	—	—	—
	III_3	46	91	9	—	—	—
	III_4	36	94	3	3	—	—
	IV	29	90	—	10	—	—

and severity of arrhythmias (table 1 and fig. 3). The only significant alteration in this group, as compared to the controls, is a decrease in the incidence and persistence of nodal and auricular rhythms. Values for stage IV have not been computed for this group as the 3 patients who exhibited the most serious arrhythmias were not carried to stage IV because of potential danger to the patient.

In contrast to the results obtained with dibenamine in doses of 5.0 to 6.0 mg. per kilogram, doses of 7.0 to 7.5 mg. per kilogram almost completely eliminated cardiac arrhythmias even in plane 4 and stage IV (table 1 and fig. 3). All types of arrhythmias were markedly reduced and the two most severe categories were completely eliminated. Abnormal supraventricular rhythms appear to be reduced even more

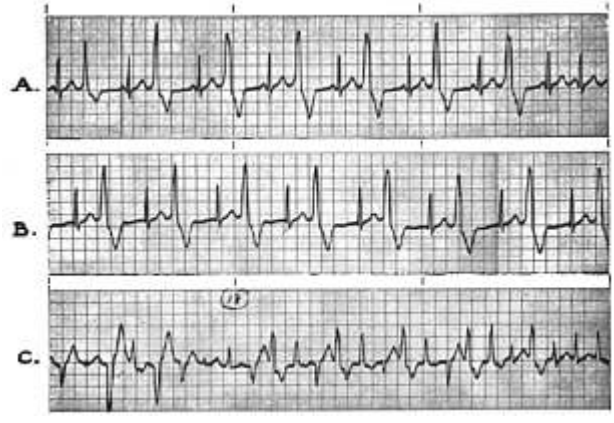

FIG. 1. Representative electrocardiograms (lead II) from control patients; plane 4 cyclopropane anesthesia. A. *Pulsus bigeminus;* alternating normal and ventricular complexes. B. *Pulsus bigeminus;* alternating nodal and ventricular complexes. C. Multifocal ventricular tachycardia.

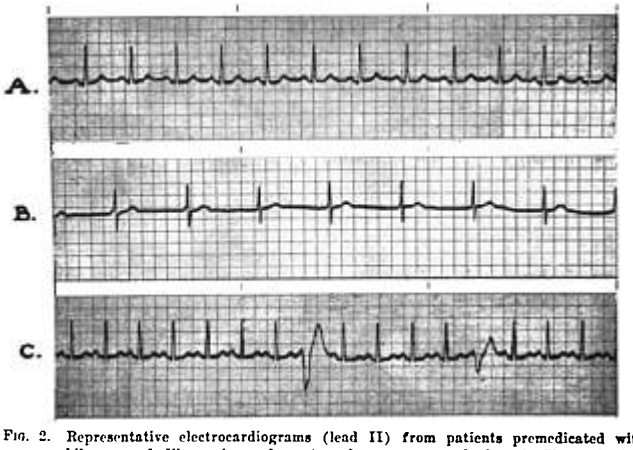

FIG. 2. Representative electrocardiograms (lead II) from patients premedicated with 7.5 mg. per kilogram of dibenamine; plane 4 cyclopropane anesthesia. A. Sinus rhythm. B. Nodal rhythm. C. Occasional ventricular complexes interspersed in a sinus rhythm.

than the ventricular types. The most severe irregularities found in any of the records from members of this group consisted only of occasional ventricular beats. The most abnormal section of record obtained from any patient in this group is shown in figure 2 C.

The correlation of the severity of arrhythmias with depth of anesthesia is shown for all three groups in figure 3.

In addition to the results obtained when the patients were well oxygenated, it was noted that short periods of hypoxia significantly increased the severity of arrhythmias in all control patients and in those receiving 5.0 to 6.0 mg. per kilogram of dibenamine. Patients treated preoperatively with dibenamine in doses of 7.0 to 7.5 mg. per kilogram

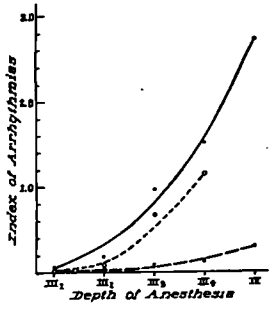

FIG. 3. Relation of cardiac arrhythmias to depth of cyclopropane anesthesia in control patients and in patients premedicated with various doses of dibenamine. See text for method of evaluating severity of arrhythmias. ●—● Controls. ○···○ Treated preoperatively with 5.0 to 6.0 mg. per kilogram of dibenamine. ●--● Treated preoperatively with 7.0 to 7.5 mg. per kilogram of dibenamine.

may also have shown some increase in the presence of hypoxia. The incidence of arrhythmias in this group, however, was extremely low under all conditions.

It has previously been reported that dibenamine has little effect on the resting blood pressures of normal animals (3, 4) and man (8, 9). In the present study the same was found to be true in the presence of the moderate stress of operation (table 2). Neither the maximum nor the minimum systolic pressure during the period of operation was altered significantly by dibenamine. The pulse pressures of patients given dibenamine preoperatively, however, were greater than those of the controls. These differences were found to be statistically significant even with the small groups involved. This increase in pulse pressure is the expected result of a blockade of sympathetic vasoconstriction with a consequent decrease in peripheral resistance. The fact that the two groups treated with dibenamine show almost identical

pulse pressures indicates that both dosages produced an essentially equal blockade of peripheral vasoconstrictor tone.

Side effects of administration of dibenamine were minimal in this series, even with doses of 7.5 mg. per kilogram, probably to a large extent because of the previous administration of a barbiturate. Only 2 patients (given 5.0 and 7.2 mg. per kilogram) experienced nausea and vomiting. About half of the patients noted some pain along the infused vein, but in many cases it was so slight that direct questioning was required to elicit the complaint. One patient noted nasal congestion after 7.5 mg. per kilogram of dibenamine, probably owing to the blockade of sympathetic vasoconstriction. Nasal congestion may have occurred more frequently than recorded, as specific questioning regarding this reaction was not undertaken. It is possible that some mental confusion attributable to the dibenamine may have occurred in a few

TABLE 2

BLOOD PRESSURES DURING OPERATION, AVERAGED BY GROUPS

Groups	Maximum		Minimum	
	Systolic/Diastolic	Pulse Pressure	Systolic/Diastolic	Pulse Pressure
Control (7 cases)	143/85	58	96/56	40
Dibenamine 5.0 to 6.0 mg. per kilogram (7 cases)	143/70	73	116/62	54
Dibenamine 7.0 to 7.5 mg. per kilogram (6 cases)	143/76	67	107/51	56

cases, but it was not sufficiently marked to be distinguished definitely from the effects of the sedative dose of barbiturate. In 2 cases in which dibenamine was given preoperatively, the operating surgeons complained of "excessive oozing." The procedures involved (open reduction of the femur and a frontal sinus operation), however, normally present difficult problems in hemostasis. It is also possible that knowledge of the use of an experimental drug in the cases involved may have affected the evaluation.

DISCUSSION

The ability of all concentrations of cyclopropane to sensitize the mammalian myocardium to the arrhythmia-inducing action of adrenergic stimuli has strongly suggested that endogenous epinephrine or sympathetic nerve activity is involved in the "spontaneous" arrhythmias noted in the clinical application of this agent. The marked protection provided by dibenamine against the irregularities encountered

in this clinical study offers confirmation of this point of view. Although dibenamine is very effective in eliminating arrhythmias caused by adrenergic stimuli, it provides only weak and transient protection against ventricular fibrillation induced by direct electrical stimulation of the myocardium, and actually increases the incidence and severity of arrhythmias after coronary occlusion (4).

In patients, and as previously observed in animal experiments (5), larger doses of dibenamine are required to prevent cardiac arrhythmias than to block and reverse the pressor effects of epinephrine and sympathetic nerve activity. Doses of 5.0 to 6.0 mg. per kilogram provide little protection against cardiac arrhythmias in the presence of cyclopropane anesthesia, although previous work on the pharmacology of this agent in human beings has demonstrated blockade and reversal of pressor responses to epinephrine and sympathetic reflexes with doses of 5 mg. per kilogram (8). In the present study the patients receiving 5.0 to 6.0 mg. per kilogram of dibenamine responded with as great an increase in pulse pressure as those receiving 7.0 to 7.5 mg. per kilogram, indicating an essentially equal blockade of peripheral vasoconstriction.

It may, therefore, be concluded that a major portion of the protection against cyclopropane-induced cardiac arrhythmias is the direct blockade of certain effects of adrenergic stimuli on the myocardium. The fact that the mean arterial pressures of the three groups during anesthesia were essentially the same (table 2) provides additional evidence that peripheral vascular effects of the drug were not major factors in the observed protection. This does not necessarily contradict the results of more detailed analyses in dogs (6, 7) which have demonstrated that inhibition of the acute rise in arterial pressure is an additional factor in the prevention of arrhythmias induced by injection of epinephrine.

The present observations on control patients quantitatively confirm the generally accepted belief that more frequent and severe arrhythmias occur in the deeper planes of cyclopropane anesthesia. The curve representing the change in incidence and severity of arrhythmias with deepening anesthesia is clearly exponential with a very rapid increase beyond plane 2. The contour of this curve strongly suggests that the severity of arrhythmias would continue to increase with even higher concentrations of cyclopropane. Danger to the patients precluded the use of such concentrations in these studies.

Side effects attributable to dibenamine were minimal. It had previously been noted that the most common side effects, which are the result of stimulation of the central nervous system, may largely be eliminated by slow infusion (9). Although most of the injections in the present series were made over a period of thirty to sixty minutes, it was found that a dose of even 7.5 mg. per kilogram was usually well tolerated when administered within a period of ten to fifteen minutes,

if preceded by sedation with barbiturates. This observation is in agreement with animal experiments which demonstrated a marked increase in the intravenous lethal dose when dibenamine was administered after barbiturate sedation (3). Although the number of cases involved is inadequate to furnish conclusive evidence regarding the effect of dibenamine on hemostasis, increased bleeding was not a prominent feature of operations performed on patients to whom dibenamine had been administered.

The fact that dibenamine prevents the operation of vasoconstrictor reflexes and the pressor effects of injected sympathomimetic agents raises questions regarding the danger of hypotension after the administration of this agent. The figures presented in table 2 indicate that significant hypotension did not occur in this small series of good-risk patients. Actually, there is reason to believe that administration of dibenamine before operation may materially lessen the dangers of "surgical shock," even though hypotension might be accentuated in some cases. Preoperative treatment with dibenamine provides marked protection against the development of irreversible shock following both hemorrhage and trauma in dogs (10, 11). This protection appears to be the result of the prevention of reflex vasoconstriction and consequent reduction in blood flow through vital organs. Although the blood pressure may actually fall more rapidly and to lower levels after administration of dibenamine, blood flow is maintained at significantly higher levels.

The slow development of the dibenamine blockade precludes the use of this agent in the treatment of arrhythmias after they have developed. Its very prolonged action, however, allows a wide margin in selecting a time for prophylactic administration.

The data presented indicate that dibenamine, in well tolerated doses, effectively prevents cardiac arrhythmias in patients under all levels of cyclopropane anesthesia. Present widespread supplementation of cyclopropane with agents such as curare and thiopental, however, has led to the routine use of much lower concentrations of the gas than were previously necessary to provide adequate relaxation. Consequently, serious cardiac irregularities are encountered much less frequently. More extensive clinical evaluation will be necessary to determine whether the routine use of an additional preanesthetic medicament is justified under present conditions. It is possible that the use of dibenamine in anesthesia will be limited to those cases in which arrhythmias are most prone to develop, for example, patients with thyrotoxicosis and those who are to have thoracic operations.

SUMMARY

Twenty healthy young adults undergoing elective surgery were carried slowly to stage IV anesthesia with unsupplemented cyclopropane. Continuous electrocardiographic tracings were taken during the

first thirty minutes or more of each anesthesia and revealed the following features:

"Spontaneous" arrhythmias occurred in all planes of anesthesia in control patients and increased exponentially as the depth of anesthesia was increased. Ominous ventricular rhythms were exhibited by all patients in plane 4 and stage IV. These arrhythmias were made more severe by hypoxia.

Preoperative treatment with dibenamine in doses of 5.0 to 6.0 mg. per kilogram caused only a slight reduction in the incidence and severity of arrhythmias.

Preoperative treatment with dibenamine in doses of 7.0 to 7.5 mg. per kilogram almost completely eliminated all arrhythmias.

Only minimal side effects of administration of dibenamine were noted in these studies. Freedom from side effects was probably attributable to a large extent to prior sedation with barbiturates.

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REFERENCES

1. Waters, R. M.: Present Status of Cyclopropane, Brit. M. J. 2: 1013–1017 (Nov.) 1936.
2. 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.
3. Nickerson, M., and Goodman, L. S.: Pharmacological Properties of New Adrenergic Blocking Agent: N,N-dibenzyl-β-chloroethylamine (Dibenamine), J. Pharmacol. & Exper. Therap. 89: 167–185 (Feb.) 1947.
4. Nickerson, M.: Pharmacology of Adrenergic Blockade, J. Pharmacol. & Exper. Therap. (Part II, Pharmacol. Rev., vol. 1) 95: 27–101 (April) 1949.
5. Nickerson, M., and Smith, S. M.: Protection Against Cyclopropane-Epinephrine Arrhythmias by Dibenamine and Other Agents, Anesthesiology 10: 562–576 (Sept.) 1949.
6. Nickerson, M., and Nomaguchi, G. M.: Mechanism of Dibenamine Protection Against Cyclopropane-Epinephrine Cardiac Arrhythmias, J. Pharmacol. & Exper. Therap. 95: 1–11 (Jan.) 1949.
7. Moe, G. K.; Malton, S. D.; Rennick, B. R., and Freyburger, W. A.: Role of Arterial Pressure in Induction of Idioventricular Rhythms Under Cyclopropane Anesthesia, J. Pharmacol. & Exper. Therap. 94: 319–327 (Nov.) 1948.
8. Hecht, H. H., and Anderson, R. B.: Influence of Dibenamine (N,N-dibenzyl-β-chloroethylamine) on Certain Functions of Sympathetic Nervous System in Man, Am. J. Med. 3: 3–17 (July) 1947.
9. Haimovici, H., and Medinets, H. E.: Effect of Dibenamine on Blood Pressure in Normotensive and Hypertensive Subjects, Proc. Soc. Exper. Biol. & Med. 67: 163–166 (Feb.) 1948.
10. Remington, J. W.; Wheeler, N. C.; Boyd, G. H., Jr., and Gaddell, H. M.: Protective Action of Dibenamine After Hemorrhage and After Muscle Trauma, Proc. Soc. Exper. Biol. & Med. 69: 150–151 (Oct.) 1948.
11. Wiggers, H. C.; Ingraham, R. C.; Roemhild, F., and Goldberg, H.: Vasoconstriction and Development of Irreversible Hemorrhagic Shock, Am. J. Physiol. 153: 511–520 (June) 1948.