

PROTECTION AGAINST CYCLOPROPANE-EPINEPHRINE
ARRHYTHMIAS BY DIBENAMINE AND OTHER AGENTS *

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MANY clinical and experimental reports have confirmed the frequent occurrence of cardiac arrhythmias during the course of cyclopropane anesthesia in man and laboratory animals. It is now well established that such irregularities occur most frequently in deeper planes of anesthesia and are often of a serious nature, including ventricular ectopic beats, multifocal ventricular tachycardias and even ventricular fibrillation. A number of anesthetic deaths of patients apparently in good physical condition have been attributed to cyclopropane arrhythmias (1).

Meek, Hathaway and Orth (2) demonstrated that all concentrations of cyclopropane sensitize the myocardium to epinephrine and that even in the absence of spontaneous arrhythmias serious irregularities may be induced by the injection of a dose of epinephrine which causes only minor irregularities in the unanesthetized animal. Their technic of injecting standard doses of epinephrine into animals under cyclopropane anesthesia has since been employed to test the ability of various agents to protect the heart against the resulting irregularities.

The ability of dibenamine (N,N-dibenzyl- β -chloroethylamine) to block many excitatory effects of epinephrine and sympathetic nerve activity (3, 4) suggested that it might provide protection against the cardiac irregularities induced by epinephrine in the presence of cyclopropane. In the experiments to be reported, various other compounds were also tested under identical conditions to provide a basis for comparative evaluation of the protection afforded by dibenamine. Preliminary reports of certain aspects of these studies have already been presented (5, 6).

METHODS

The method employed to produce cardiac arrhythmias was a modification of that originally reported by Meek, Hathaway and Orth (2). Dogs were given sufficient thiopental sodium intravenously, usually 15

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to 20 mg. per kilogram, to allow tracheal intubation to be performed. An anesthetic mixture of 30 per cent cyclopropane and 70 per cent oxygen was then administered by means of a closed system with carbon dioxide absorption. A total gas flow of 1,000 cc. per minute was maintained. The 3 liter rebreathing bag was frequently flushed, and analysis of the gas mixture showed the cyclopropane concentration in the bag to vary between 28 and 31 per cent. This procedure maintained most unmedicated dogs in plane 3 anesthesia (partial to complete intercostal paralysis). After the administration of certain protective agents (especially meperidine and ergotamine), spontaneous respiratory exchange became inadequate and oxygenation was maintained by intermittent pressure on the rebreathing bag. All tests were performed after thirty to sixty minutes of cyclopropane anesthesia to allow for complete equilibration and yet to avoid the "adrenolytic" effect of longer exposures to cyclopropane (7).

After equilibration to the anesthetic mixture, a standard challenge dose of 10 microgram per kilogram of epinephrine in 5 milliliters of 0.9 per cent sodium chloride was injected into a foreleg vein at a uniform rate over a period of fifty seconds. Unless fatal ventricular fibrillation supervened, the entire test dose was administered, although ventricular tachycardia usually developed after about one-half of the amount had been injected. In certain cases larger doses of epinephrine were employed, as noted below.

Standard limb lead electrocardiograms were begun before epinephrine was injected and continued until the control rate and rhythm had returned. In most cases, three leads were recorded simultaneously using a thermowriting oscillograph. From these records were determined the total duration of irregularities (including abnormalities of impulse origin and major abnormalities of conduction, but excluding T wave and S-T segment changes), the duration of ventricular tachycardia, and the cardiac rates before, during and after the irregularities.

Protective agents were administered intravenously ten to thirty minutes before the challenge dose of epinephrine.

During the course of these studies a seasonal variation in the severity of epinephrine-cyclopropane arrhythmias in control animals was noted. To avoid complications arising from this factor the control and experimental animals reported below were studied during comparable seasons.

A total of 134 experiments was performed on 84 dogs. Some animals were tested with more than one protective agent. In these dogs an interval of one week or more was always allowed between experiments.

RESULTS

Electrocardiograms from control animals showed that the first irregularity (usually a ventricular premature systole) occurred an average of sixteen seconds after the beginning of epinephrine injection.

This interval is probably approximately equal to the foreleg-coronary circulation time. Only slight acceleration of the sinus rate preceded the first irregularity. When it occurred (fig. 1, A), ventricular fibrillation began an average of eight seconds after the first irregularity. The interval between the first irregularity and the beginning of fibrillation was essentially the same for those animals in which fibrillation occurred after various types of premedication. In only one case in the entire series was this interval greater than twenty seconds.

Ventricular fibrillation was uniformly fatal except in 2 animals in which short bursts of fibrillation (less than two seconds' duration) reverted spontaneously to ventricular tachycardia. Various procedures, including open-chest cardiac massage and intracardial and epicardial application of 2 per cent procaine hydrochloride, were used in an effort to stop ventricular fibrillation, but all fourteen attempts in this series were unsuccessful.

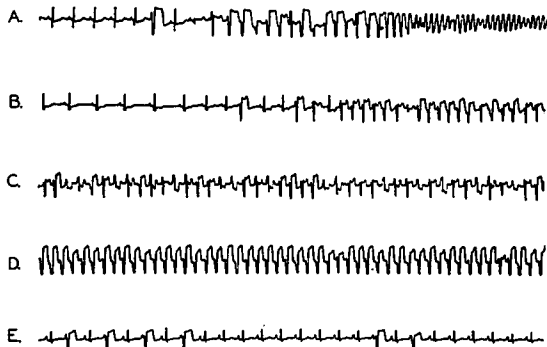


FIG. 1. Electrocardiograms (lead II) showing cardiac response of unpremedicated dogs under cyclopropane anesthesia to the intravenous injection of 10 μ g. per kilogram of epinephrine. A. Animal developing ventricular extra systoles, ventricular tachycardia and ventricular fibrillation. B and C. Animal developing multifocal ventricular tachycardia which was followed by recovery. D. Section of record showing a uniform ventricular tachycardia; one minute after the beginning of the epinephrine injection. E. Record from same animal as D, two and a half minutes after beginning injection of epinephrine showing reversion to sinus rhythm.

In control animals in which fibrillation did not take place, ventricular tachycardia developed about four seconds after the first irregularity and continued for an average of ninety-one seconds. In a few tests the ventricular tachycardia was interrupted by two or three short periods of nodal or sinus rhythm. This tachycardia was usually multifocal in nature (fig. 1, B and C), but a few cases showed long periods of rather uniform ventricular rhythm (fig. 1, D). Irregularities (fig. 1, E),

particularly ectopic beats, pulsus bigeminus or nodal rhythm, usually continued for some time after the end of frank ventricular tachycardia.

Significant mean values and their standard errors for control and experimental animals with respect to the duration of irregularities and of ventricular tachycardia are shown in tables 1 and 2. It is recognized that the numbers of animals in some of the groups are small and at the lower limits of validity of the statistical methods employed. However, use of the factor $n-1$ in calculating the standard deviation tends to correct for the smaller groups and all differences greater than two times the standard error of the difference are probably significant. It is possible that in some series a larger number of animals might reveal additional minor but significant effects.



FIG. 2. Electrocardiograms (lead II) of dogs under cyclopropane anesthesia after various types of premedication showing cardiac response to the intravenous injection of 10 μ g. per kilogram of epinephrine. A and B. After 20 mg. per kilogram of dibenamine. A few ectopic beats such as seen in B occurred in only 5 of 28 animals tested. C and D. After 1.0 mg. per kilogram of atropine sulfate, showing slow, progressive changes in form. C begins fifteen seconds and D forty-five seconds after the beginning of injection of epinephrine in two different animals. E. After 0.25 mg. per kilogram of ergotamine tartrate, forty seconds after the beginning of injection of epinephrine.

Dibenamine hydrochloride was administered intravenously in doses of 20 mg. per kilogram. Preliminary experiments indicated that maximum protection against cyclopropane-epinephrine cardiac irregularities required larger doses of dibenamine than are necessary to block the pressor response to epinephrine. The drug was administered thirty minutes before the test dose of epinephrine, as previous work (3, 4) demonstrated that at least thirty minutes is required for dibenamine to develop its full effect after intravenous administration.

Pretreatment with dibenamine almost completely eliminated the epinephrine-induced cardiac irregularities (table 1). Only 5 of 28 animals developed any arrhythmia, and the only type of irregularity

observed was occasional ventricular beats (fig. 2, B). The number of ectopic beats varied from 1 to a maximum of 15, in the latter case scattered over a period of twenty-five seconds. Dibenamine did not significantly alter the period of time required for the heart to return to its normal rate after the injection of epinephrine. Previous experiments (3, 4) indicated that the increase stroke volume and cardiac output following injection of epinephrine are also unaltered by dibenamine. Therefore, it appears that the only cardiac action of epinephrine studied to date which is blocked by dibenamine is the production of irregularities.

When tested with a challenge dose of epinephrine (100 microgram per kilogram) ten times greater than usually employed, animals treated with dibenamine showed no significant increase in the incidence or severity of the irregularities (table 1). In several animals, injections of even 100 or 1,000 times the standard dose of epinephrine were made without the development of arrhythmias. This large margin of safety provided by dibenamine is in agreement with the previously demonstrated completeness of the dibenamine block of other excitatory actions of epinephrine (3, 4, 8).

TABLE 1
INCIDENCE OF ARRHYTHMIAS IN DOGS PREMEDICATED WITH DIBENAMINE AND PRISCOL

Treatment	Dose mg./kg.	No. Animals	Ventricular Fibrillation	Total Duration of Arrhythmias* Seconds	Duration of Ventricular Tachycardia* Seconds
10 μ g./kg. of Epinephrine					
Control	—	25	32%	145 \pm 7.2	91 \pm 9.6
Dibenamine hydrochloride	20	23	0	1.8 \pm 1.0	0
Priscol hydrochloride	20	8	0	3 \pm 2.0	0
Compound No. 12	20	5	40%	107 \pm 7.1	96 \pm 5.0
Compound No. 178	10	6	33%	132 \pm 21	113 \pm 12
100 μ g./kg. of Epinephrine					
Dibenamine hydrochloride	20	16	0	3 \pm 1.8	0
Priscol hydrochloride	20	6	17%	65 \pm 15	25 \pm 8.4

* In dogs not developing ventricular fibrillation.

In animals treated with dibenamine, the increased heart rate before injection of epinephrine (table 3) is largely secondary to a moderate fall in blood pressure. This fall in pressure may be small or absent if the dibenamine is given to anesthetized animals by slow infusion (3, 4). In the present experiments the drug was injected rather rapidly as a matter of convenience since the anesthetic eliminated any danger from central nervous system stimulation which may accompany rapid injection in unanesthetized animals. In these experiments dibenamine produced only a moderate increase in respiratory exchange.

Two compounds with a close structural relationship to dibenamine, but without adrenergic blocking action, were also tested. In these compounds the β -chloroethyl group of dibenamine is replaced by a methyl group (No. 178) or by a β -hydroxyethyl group (No. 12). Compound No. 12 in 20 mg. per kilogram doses provided a slight reduction in the total duration of irregularities, but had no significant effect on the duration of ventricular tachycardia. Compound No. 178 provided no protection and may even have increased the average period of ventricular tachycardia. Doses of No. 178 greater than 10 mg. per kilogram could not be administered because of the high toxicity of the compound. Even with doses of 10 mg. per kilogram, 2 of 6 animals died on the second day after administration.

Compound No. 178 was reported by Moisset de Espanés and Weksler (9) to be effective in preventing electrically-induced fibrillation. Its failure to protect against cyclopropane-epinephrine cardiac irregularities emphasizes the fact that protection against electrically-induced fibrillation is no index of potential protection against irregularities arising in response to adrenergic stimulation in a myocardium sensitized by an anesthetic agent.

Priscol hydrochloride (2-benzyl-imidazoline) * was administered intravenously ten to twenty minutes prior to the test dose of epinephrine. Preliminary observations indicated that 5 mg. per kilogram gave only very limited protection. A dose of 20 microgram per kilogram was selected for study in order to assure maximum drug action, although considerably smaller doses of priscol have been shown to possess adrenergic blocking action, both in our laboratory and by others (10, 11).

Under the conditions of these experiments priscol provided almost complete protection against the irregularities caused by the standard 10 mg. per kilogram dose of epinephrine. Irregularities, consisting of occasional ventricular extra systoles, occurred in 2 of 6 animals. In the remaining animals only a sinus tachycardia developed.

When larger doses of epinephrine (100 mg. per kilogram) were administered, priscol provided only limited protection (table 1). This contrasts sharply with the essentially complete protection afforded by dibenamine against all doses of epinephrine. The difference is probably an expression of the much greater adrenergic-blocking effectiveness of dibenamine.

Animals treated with priscol secreted large amounts of mucus in the respiratory tract which made the maintenance of adequate respiratory exchange difficult. Even smaller doses of priscol than those employed here have been reported to stimulate salivary secretion (11). Priscol also caused marked sinus tachycardia (table 3), primarily by a direct cardiac action (12).

Ergotamine tartrate and dihydroergotamine methanesulfonate have been reported to provide considerable protection against cyclopropane-

* Kindly supplied by Dr. F. F. Youkman of Ciba Pharmaceutical Products, Inc.

epinephrine irregularities (13, 14). Under the conditions of our experiments, 0.25 mg. per kilogram of ergotamine tartrate provided only slight, although probably significant, protection. Because of the small number of animals involved, the reduced incidence of fibrillation is not significant. Larger doses of ergotamine could not be tested because of their high toxicity. The dose employed caused respiratory arrest during cyclopropane equilibration in all of the animals tested and one animal could not be revived at the end of the experiment although ventricular fibrillation had not occurred. The cardiac toxicity of ergotamine was indicated by a widening of the QRS complex and bizarre rhythms in the presence of epinephrine. An example of the more severe toxic arrhythmias occurring in the presence of ergotamine is illustrated in figure 2, E. Manning and Caudwell (15) noted similar cardiac irregularities as well as peripheral vascular collapse and prostration in unanesthetized dogs administered the same dose of ergotamine.

TABLE 2
INCIDENCE OF ARRHYTHMIAS IN DOGS PREMEDICATED WITH VARIOUS AGENTS
WITHOUT SIGNIFICANT ADRENERGIC BLOCKING ACTIVITY

Treatment	Dose mg./kg.	No. Animals	Ventricular Fibrillation	Total Duration of Arrhythmias* Seconds	Duration of Ventricular Tachycardia* Seconds
Control	—	25	32%	145±7.2	91±9.6
Meperidine hydrochloride	10	12	8%	77±16	33±9.5
Procaine hydrochloride	15	16	19%	94±13	60±12
Ergotamine tartrate	0.25	8	0	104±9.5	46±11
Atropine sulfate	1.0	14	21%	73±18	44±12
Atropine sulfate	0.1	8	13%	112±21	67±20
Quinidine sulfate	5	6	17%	93±14	72±10

* In dogs not developing ventricular fibrillation.

Ergotamine and meperidine were the only agents studied which markedly delayed the onset of cardiac irregularities. However, after treatment with ergotamine a considerable part of this delay is apparently due to circulatory slowing. Once epinephrine did reach the heart, as indicated by sinus tachycardia, arrhythmias usually developed within a few seconds.

Although ergot alkaloids are classified as adrenergic blocking agents, the blocking action of ergotamine is relatively weak and clear-cut reversal of the pressor action of epinephrine in animals under most types of anesthesia is demonstrable only with doses considerably larger than those employed in these experiments. With dibenamine and priscol, both more effective adrenergic blocking agents than ergotamine, larger doses were required to block cyclopropane-epinephrine arrhythmias than to block most other excitatory actions of epinephrine. Therefore, it seems probable that the observed protection against cyclopropane-epinephrine irregularities is the result of a generalized

myocardial depression (as suggested by the electrocardiogram) rather than of a specific adrenergic blocking action. Additional evidence for this conclusion is the fact that Orth and Ritchie (14) found larger doses of dihydroergotamine than of ergotamine were required to protect against cardiac irregularities, although the former is the more potent adrenergic blocking agent (16).

Atropine sulfate was tested at two dose levels, 0.1 mg. per kilogram (adequate to block completely cardiac slowing following maximal vagal stimulation in dogs) and 1.0 mg. per kilogram. The former dose provided no significant protection, although the sinus tachycardia before the administration of epinephrine (table 3) indicated that vagal effects were eliminated as completely as with the larger dose of atropine.

TABLE 3
HEART RATES AND TIME OF ONSET OF ARRHYTHMIAS IN DOGS PREMEDICATED
WITH VARIOUS AGENTS

Treatment	Dose mg./kg.	No. Animals	Onset of Arrhythmias*	Control Heart Rate	Maximum Sinus Tachycardia
10 μ g./kg. of Epinephrine					
Control	—	25	16 \pm 0.7	153 \pm 6.0	175 \pm 5.9
Meperidine hydrochloride	10	12	37 \pm 3.3	118 \pm 7.3	169 \pm 6.4
Procaine hydrochloride	15	16	23 \pm 3.2	153 \pm 7.2	208 \pm 11
Ergotamine tartrate	0.25	8	36 \pm 9.2	103 \pm 10	147 \pm 18
Atropine sulfate	1.0	14	17 \pm 1.2	182 \pm 7.5	234 \pm 12
Atropine sulfate	0.1	8	16 \pm 1.4	181 \pm 16	217 \pm 18
Quinidine sulfate	5	6	21 \pm 3.1	137 \pm 8.9	172 \pm 9.9
Dibenamine hydrochloride	20	28	16 \pm 1.7	167 \pm 8.3	254 \pm 6.9
Prisol hydrochloride	20	6	18	191 \pm 26	244 \pm 15
Compound No. 12	20	5	17 \pm 1.6	153 \pm 9.5	165 \pm 14
Compound No. 178	10	6	20 \pm 2.9	135 \pm 12	180 \pm 9.4
100 μ g./kg. of Epinephrine					
Dibenamine hydrochloride	20	16	14 \pm 1.8	178 \pm 9.2	294 \pm 6.6
Prisol hydrochloride	20	6	17 \pm 1.3	190 \pm 17	243 \pm 15

* In dogs developing arrhythmias.

Epinephrine-induced arrhythmias were considerably reduced by atropine in doses of 1.0 mg. per kilogram. This protection is undoubtedly significant although the degree of protection varied widely with different animals, as is reflected in the rather large standard errors of the mean values for the duration of irregularities and of ventricular tachycardia.

The protection afforded by atropine against epinephrine-induced cardiac irregularities both in anesthetized and unanesthetized animals has been attributed by several workers to block of the vagus (17, 18). It is assumed by these workers that irregularities result from the

simultaneous stimulation of the myocardium by epinephrine and depression of the S-A node by reflex discharge of the vagus (secondary to the pressor effect of epinephrine), allowing ventricular foci to escape from control of the pacemaker. Elimination of vagal effects by atropine or vagotomy might, therefore, prevent irregularities by allowing the S-A node to maintain its dominance over the ventricles.

Although the blocking of vagal impulses cannot at present be eliminated as a minor factor in the prevention of epinephrine-induced cardiac irregularities, the major protective action in the presence of both sensitizing and nonsensitizing anesthetics appears to be due to some direction action on the myocardium exerted by large doses of atropine (6). This is in agreement with the early work of Levy (19) on chloroform-induced cardiac arrhythmias. It should be emphasized that the dose of atropine necessary to provide significant protection in these experiments is about 150 times as great, on a weight basis, as that usually employed clinically.

Meperidine hydrochloride (demerol) in doses of 10 mg. per kilogram was administered intravenously about fifteen minutes before the test dose of epinephrine. The combined depressant effects of this agent and cyclopropane caused respiratory arrest in 10 of 12 dogs, but adequate respiratory exchange was maintained by manual compression of the rebreathing bag. Treatment with meperidine caused marked reduction in the duration of both the total irregularities and the ventricular tachycardia. The average time from the beginning of the injection of epinephrine to the first irregularity was also increased (from sixteen seconds in the controls to thirty-seven seconds). This delay does not appear to be due primarily to an increased circulation time and the first sign of cardiac stimulation (sinus tachycardia) appears some time before the irregularities. In some animals, a brief period of nodal rhythm developed shortly after the epinephrine reached the heart, but in all cases this reverted to a sinus tachycardia before the advent of more serious irregularities. A large part of the delay in the appearance of arrhythmias may therefore be attributed to an increased cardiac resistance to the epinephrine action. The marked cardiac slowing caused by meperidine (table 3) is in agreement with previous observations of Robbins (20).

Robbins (20) noted that meperidine prevented "spontaneous" cardiac arrhythmias under cyclopropane anesthesia. In our experiments this agent also provided considerable protection against arrhythmias induced by the severe stress of injected epinephrine. Except for the adrenergic blocking drugs dibenamine and priscol, it provided the greatest protection of any agent tested. Meperidine is now widely accepted as a useful agent for preanesthetic medication and its action in preventing cardiac arrhythmias may represent an additional advantage over morphine, which may actually increase the incidence of arrhythmias under certain conditions (21).

Procaine hydrochloride, in doses of 10 mg. per kilogram, was administered ten to fifteen minutes before the challenge dose of epinephrine. With this time interval the protection afforded was not impressive, being just within the range of significance. The animals tested after a ten-minute interval seemed to be better protected than those tested at fifteen minutes.

Although Burstein and co-workers (22) reported that intracardiac procaine was effective in stopping ventricular fibrillation in a large percentage of animals, this treatment did not restore an effective beat in a single animal in our series. In 14 animals procaine (by intracardiac injection of up to 50 mg. per kilogram and epicardial application of a 2 per cent solution) failed to bring about reversion to a normal rhythm even when given within thirty seconds of the onset of fibrillation and accompanied by cardiac massage to maintain circulation. The present results agree with those of Stutzman et al. (23).

In contrast to the negative results obtained in ventricular fibrillation, procaine is effective in stopping ventricular extra systoles and ventricular tachycardia (24), as indicated by clinical experience (25, 26). It is possible that failure to distinguish between a very rapid and uniform ventricular tachycardia and ventricular fibrillation may account for the reported efficacy of procaine in stopping the latter (23).

The short duration of the protection afforded by procaine points to a limited prophylactic value. However, as noted above, it is effective both in animals and in man in restoring a sinus rhythm after irregularities other than ventricular fibrillation have developed.

Quinidine sulfate in doses of 5 mg. per kilogram administered ten to twenty-five minutes before testing was found to provide only slight protection against cyclopropane-epinephrine arrhythmias. Doses of 10 or 15 mg. per kilogram offered clear-cut protection, as previously demonstrated (13). However, 5 mg. per kilogram was selected for study because this dose was shown by Wégria and Nickerson (27) to provide marked protection against electrically-induced fibrillation.

The limited protection observed in the present experiments indicates that electrically-induced fibrillation is quite different from the cardiac irregularities and fibrillation induced by epinephrine in the presence of certain anesthetic agents. This point was even more clearly illustrated by the behavior of certain congeners of dibenamine (see above). Non-specific myocardial depression appears to be a more important factor in protection against the former than the latter.

DISCUSSION

In the experiments reported, an effort was made to utilize as severe a cardiac stress as possible in order to provide maximum differentiation of the protective actions of the various agents. Animals were tested during the period of maximum sensitivity (after about thirty minutes'

exposure to cyclopropane) and the entire 10 microgram per kilogram test dose of epinephrine was injected irrespective of when the first irregularities appeared. Although the thiopental used for induction was largely destroyed before testing, any residual effect was probably in the direction of increasing the severity of the arrhythmias (28). Under these conditions, compounds which might have provided considerable protection against a less severe stress showed only minor activity.

The data obtained in these experiments do not supply any common denominator to explain the protection afforded by various agents. Data in table 3 indicate that both the control heart rate and the maximum sinus tachycardia developing prior to the appearance of irregularities are roughly correlated with the degree of protection. This might be expected on the basis that a very rapid sinus rate would tend to suppress the activity of ectopic foci. However, the absence of protection after small doses of atropine and the marked protection afforded by meperidine are major exceptions to the relation of sinus rate to protection.

With the exception of meperidine and ergotamine, all agents producing reduction in the total duration of irregularities and in the duration of ventricular tachycardia did so primarily by causing an earlier cessation rather than a delayed onset of arrhythmias. Even with compounds providing maximum protection (dibenamine, priscol), the few irregularities which did occur began as soon as the epinephrine reached the heart.

This observation has two important implications. First, a sudden increase in epinephrine concentration rather than the total concentration of epinephrine appears to be the more important factor in initiating cardiac irregularities. The maximum epinephrine concentration in blood reaching the heart must occur shortly after the end of the injection, but no irregularities of any kind occurred at this time in animals treated with either dibenamine or priscol and tested with the standard dose of epinephrine. Some type of accommodation to epinephrine action seems to occur, perhaps as a result of the positive inotropic action of epinephrine or changes in coronary circulation (see discussion 29, 30). The second implication is that the peripheral actions of epinephrine (vasopressor effect, reflex activation of the vagus, and so forth) are not of primary importance in the development of arrhythmias, since the maximum tendency to develop irregularities occurs before the injected epinephrine has been widely distributed to the peripheral circulation. The maximum pressor effect occurs between one and two minutes after the beginning of the epinephrine injection.

Certain features of the electrocardiographic changes noted in the above experiments deserve special mention. After the administration of dibenamine or priscol the effects of large doses of epinephrine on the electrocardiogram may be observed without the usual complications of ectopic beats and reflex vagal action. In general, the changes

observed were extensions of the changes noted with smaller doses of epinephrine in both experimental animals and human beings (31, 32, 33). One of the first effects of epinephrine was usually a depression of the S-T segment. During the recovery phase, however, the depression of the S-T segment was usually less than that observed in control animals immediately after the cessation of irregularities. The T wave showed less consistent depression than the S-T segment and a transient increase in amplitude almost always occurred during the early stages of epinephrine action.

At the height of the epinephrine action the absolute duration of the "electrical systole" (Q-T) was always considerably reduced from the control value. Although the electrical systole (Q-T) is not an exact measure of the mechanical systole (34), this reduction is in agreement with the known effect of epinephrine in shortening the mechanical systole (35). As noted by Hecht and Anderson (33), when smaller doses of epinephrine were given to patients pretreated with dibenamine, the relative Q-T (Q-T/R-R ratio) was increased during the epinephrine tachycardia. This increase closely paralleled the cardiac rate and was not specific for epinephrine as it was also observed in the tachycardia seen after the administration of priscol (table 3). A similar increase in the relative Q-T has been observed during cardiac acceleration resulting from exercise (36). In all cases, the prolongation of the relative Q-T is probably merely the electrical expression of the well-known fact that with increased rate, cardiac systole is shortened less than diastole.

The irregularities induced by epinephrine after large (1.0 mg. per kilogram) doses of atropine are particularly difficult to interpret. The abrupt change from a normal sinus rhythm to ventricular beats or ventricular tachycardia seen in control animals (fig. 1, A and B) and in all other groups in this study rarely occurs. Instead, the changes develop gradually (fig. 2, C and D) and many of the resulting electrocardiographic complexes are so bizarre that it is impossible to determine the point of origin of the impulse. Abnormalities of both impulse formation and conduction are probably involved but their exact basis is obscure. Similar slow changes were observed less frequently in animals pretreated with small (0.1 mg. per kilogram) doses of atropine.

Compounds studied in these experiments may be divided into two classes: agents without significant adrenergic blocking action (including ergotamine which has little blocking action in tolerated doses) and active adrenergic blocking agents. In the former group, meperidine seems to be the only really promising agent and probably deserves clinical study of its ability to prevent cardiac irregularities under cyclopropane anesthesia. Procaine requires special mention. Although the action of single doses is too transient to be of prophylactic value, it is effective in stopping irregularities other than ventricular fibrillation. Our results confirm the failure of this agent to stop ventricular fibrillation once it has developed. It seems probable that all compounds of

this group (including large doses of atropine and tolerated doses of ergotamine) act through nonspecific myocardial depression.

The effective adrenergic blocking agents in this series are dibenamine and priscol, which provide much greater protection against epinephrine-cyclopropane cardiac irregularities than the other compounds studied. The fact that larger doses of either of these agents are required consistently to eliminate cardiac irregularities than to reverse the pressor effects of the same dose of epinephrine indicates that the peripheral action of these agents in preventing the pressor response to epinephrine is not the essential factor, although it may contribute to the protection. This conclusion is in agreement with the results of more detailed studies on the mode of action of dibenamine (30).

The marked protection against cyclopropane-epinephrine cardiac irregularities afforded by the adrenergic blocking agents included in this study, particularly dibenamine, suggests that they might be useful clinically in preventing "spontaneous" cardiac irregularities occurring during cyclopropane anesthesia. The present widespread use of curare and thiopental to supplement cyclopropane has led to the routine use of much lower concentrations of the latter agent than were previously employed. Serious irregularities are consequently less common than formerly. Arrhythmias still occur, however, and a detailed clinical study will be necessary to determine whether the elimination of these irregularities is of sufficient value to warrant the use of additional pre-anesthetic agents which may in themselves produce certain undesirable side effects. Preliminary clinical studies involving the prophylactic administration of dibenamine before cyclopropane anesthesia (37) have already indicated that dibenamine is effective in almost completely eliminating cyclopropane-induced arrhythmias in surgical patients.

The work of Manning and Caudwell (15) indicates that 0.25 mg. per kilogram of ergotamine tartrate or 0.5 mg. per kilogram of dihydro-ergotamine methanesulfonate offers considerable protection against immediate death (ventricular fibrillation) occurring after acute coronary occlusion in dogs. However, the relatively high toxicity/adrenergic blocking ratio for these compounds, especially ergotamine, probably prevented the development of an effective adrenergic blockade in their animals. Although the role of adrenergic blockade in the protection afforded by these ergot alkaloids is not clear, the marked protection against ventricular fibrillation and other cardiac arrhythmias provided by the dibenamine and priscol suggests that a trial be made of their ability to protect against the ventricular fibrillation occurring after coronary occlusion.

SUMMARY

The ability of various drugs to protect against epinephrine-induced cardiac irregularities was tested in dogs under cyclopropane anesthesia.

Meperidine and large doses of atropine were found to provide considerable protection, while quinidine, ergotamine and procaine provided slight protection. The short duration of action of procaine is largely responsible for limiting its prophylactic effectiveness. Small doses of atropine (adequate to block the cardiac effects of vagal stimulation) offered no protection. It is concluded that such protection as is afforded by the above agents is on the basis of nonspecific myocardial depression.

The active adrenergic blocking agents dibenamine and priscol provided essentially complete protection against irregularities induced by the standard test dose of epinephrine. This protective action was not exerted by congeners lacking adrenergic blocking activity. Dibenamine, but not priscol, also provided complete protection against multiples (as high as 1,000) of the standard dose.

Certain practical and theoretical implications of the protection against cardiac arrhythmias afforded by these drugs are discussed.

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