A NEW METHOD FOR EXPERIMENTAL EVALUATION OF DRUGS FOR USE IN CHRONIC ATRIAL FIBRILLATION

By

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A THESIS

Presented to the Department of Pharmacology
and the Graduate Division of the
University of Oregon Medical School
in partial fulfillment of the
requirements for the degree of
Master of Science

June, 1957

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(Professor in Charge of Thesis)

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(Chairman, Graduate Council)

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ACKNOWLEDGEMENTS

The counsel and encouragement of Doctor Elton L. McCawley and Doctor H. L. H. Dick is gratefully acknowledged. I wish to thank Doctor Norman A. David for his help during the experiments and preparation of this manuscript.

Financial support for these studies was supplied by a grant-in-aid from the National Institute of Health through the National Heart Institute. The author realizes that without the aid of a fellowship from the National Heart Institute and from Parke-Davis and Company, this rewarding experience in research would have been impossible.

I wish to thank Doctor A. C. Bratton, Jr., Parke-Davis and Company for the camoquin derivatives; Doctor Gordon A. Alles, The Alles Laboratories, for the allocryptopine; and Doctor R. F. Manske, The Dominion Rubber Company, Limited, for the corycavine used in these experiments.

INTRODUCTION

Atrial fibrillation has received considerable attention since Hering's classical description* (1) in 1903. This disorder today is recognized as the most common cardiac arrhythmia of clinical significance (2 - 5) yet its pathogenesis is now no better understood than it was fifty years ago. When H. E. Hering stated that, "the pulsus irregularis perpetuus is due to an irregularity of the heart of myogenic origin produced by extra stimuli", he circumscribed the extent of present day knowledge concerning the pathogenesis of this condition.

DiPalma (6) states that significant advances in anti-fibrillatory drugs cannot be expected until the mechanisms by which these drugs act are recognized. It is obvious that in order to understand the mechanism of a drug's action, the underlying factors responsible for the disease must also be known. Since, for atrial fibrillation, we understand neither the action of the drug nor the mechanismscausing the arrhythmia, progress in the therapy of this disease must necessarily be limited. As a corollary, if we but knew the one property common to all agents effective in the therapy of atrial fibrillation, additional knowledge basic to the pathogenesis of this arrhythmia would be achieved.

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*Atrial fibrillation as an irregular pulse was originally described in 1705 by Raymond Vieussens in his report on a patient with mitral stenosis.

CLINICAL IMPORTANCE OF ATRIAL FIBRILLATION

It is well known that patients with various types of cardiac disease also have atrial fibrillation. (2 - 5) (7 - 9) Many workers in the field refer to the underlying cardiac difficulty as the "etiology" of the arrhythmia. This is only etymologically correct.

It has been stated that 60 - 90 per cent of persons with congestive heart failure will manifest atrial fibrillation sometime during the course of their illness. (4) (10) (11) A certain number of these will spontaneously revert to normal sinus rhythm. One group of investigators using quinidine sulfate as an antifibrillatory agent was able to convert 53 per cent of their patients. (11) Results from other studies vary widely, with a range from 30 to 90 per cent and a mean of 70 per cent, depending on the type and degree of underlying cardiac pathology. (7) (11 - 13) Others contend that the type of heart disease is not a factor. (14) (15) In order to maintain normal sinus rhythm a daily maintenance dose of quinidine was required in the majority of cases. Patients with a past history of decompensation were more difficult to convert and to maintain than those patients who had no previous history of cardiac failure. (7) (11) Equally convincing arguments can be advanced for an association of rheumatic heart disease with atrial fibrillation. Of patients with atrial fibrillation, 50 per cent had a history of rheumatic mitral insufficiency. (11) Mitral commissurotomy for mitral stenosis is commonly followed by the appearance of atrial fibrillation. (8) (16)

Finally, untreated thyrotoxicosis is associated with atrial fibrillation and the arrhythmia cannot be converted to sinus rhythm by quinidine until the thyroid disorder is corrected. (9)

Two facts, however, destroy much of these attractive arguments. It is well known that some patients have atrial fibrillation, of both the paroxysmal and persistent types, without any associated heart disease. (17 - 25) Moreover, many patients with frank cardiac disease (congestive heart failure, rheumatic valvulitis, or thyrotoxic heart disease) do not have atrial fibrillation at all, but rather a normal sinus rhythm. Thus other more subtle biochemical or functional changes of the heart must be explored as a basis for atrial fibrillation.

It is pertinent to discuss what little is known of the pathophysiology of atrial fibrillation. The extent of the adverse effects of this arrhythmia will of course be modified by the condition of the patient. Phillips and Levine (26) discuss the abnormal circulatory dynamics in atrial fibrillation without other evidence of heart disease. The work of these authors is supported by others who have done studies on fibrillating animals and human subjects. (27 - 30) All are agreed that the rate of blood flow as measured by the circulation time is definitely decreased during atrial fibrillation. As would be expected, the cardiac out put is decreased, by as much as 40 per cent in some cases. (31) That the impaired circulation could not be ascribed to an increase in heart rate was evident from the fact that cardiac output and rate of flow of blood were greater in sinus tachycardia, but decreased in atrial fibrillation at the same heart rate. (26) The rate of venous flow in these animals returned to normal after conversion to normal sinus rhythm.

While it is quite likely that the irregular filling of the left ventricle during diastole accounts for the major portion of the circulatory deficit, there is still another factor to consider. Daley

and McMillan (32) in 1955 demonstrated mitral insufficiency in animals with experimentally induced atrial fibrillation. Perhaps this incompetence of the mitral valve plays a major role in the decrease in cardiac output and diminished stroke volume, and the increased pulmonary artery pressure which has been demonstrated. (27) These changes were all eliminated when conversion to normal sinus rhythm was achieved.

It is thus obvious that this arrythmia will be a particular burden to the patient in congestive heart failure who needs all available help in maintaining his cardiac output and blood pressure. The effect of atrial fibrillation on blood pressure and cardiac output in patients with congestive heart failure has been studied. (29) The findings are in agreement with what has been stated previously.

A patient with congestive heart failure and atrial fibrillation may have his ventricular rate controlled with digitalis. The circulatory dynamics at rest may meet physiological requirements. However, the digitalized, fibrillating patient cannot increase cardiac output by controlling the ventricular rate. (26) (33) (34) Consequently, these patients may experience syncope, dyspnea, dizziness and other symptoms in response to increased activity or emotional stress. If the atrial musculature were functioning normally and its activity under vagal control, the patient would be more physiologically compensated. Finally, it is not unusual to find fibrillating patients with congestive heart failure who cannot be compensated until normal sinus rhythm is restored, even though adequately digitalized. (26) (35) (36) It is fallacy to assume that simply reducing the ventricular rate to 60 - 80 beats per minute with digitalization solves the patient's cardiac problem.

If the deleterious effects of this arrhthmia were simply physiological it would provide reason enough for attempt at conversion. There is, however, another important factor to consider and that is systemic embolization.

There has been considerable controversy whether or not patients who have been fibrillating for any period of time should be converted to normal sinus rhythm. The proclivity on the part of many clinicians to allow patients to continue with their arrhythmia in order to avoid systemic emboli has been fostered by the misconception that the incidence of embolic episodes is increased at the time of conversion. (37) (38) Several recent studies refute this belief. (2) (7) (8) (39) (40) One states the likelihood of a patient discharging an embolus was seven times greater if the atrial fibrillation were allowed to continue than if conversion to sinus rhythm had been achieved. (12) It must also be borne in mind that with the use of anticoagulants ten to fourteen days prior to starting quinidine, there is considerably lesser possibility of embolization. (7) (12) (40)

The importance of adopting a course or procedure which results in the least number of embolic episodes can be seen from the following report. (40) In this series of 194 patients with atrial fibrillation, there were 393 emboli; 50 per cent of these were cerebral and resulted in 50 per cent mortality. In addition, 17 per cent involved the lower extremity and 10 per cent the upper extremity. These statistics are reflected in other reports. (7) (8) (35) (41) (42) While it is known that systemic emboli may occur following coronary occlusion or myocarditis with mural thrombi, (8) (43) (44), 80 to 90 per cent of these emboli are in patients

with atrial fibrillation; (7) (40) (42) either alone or in conjunction with other cardiac pathology.

The possibility of pulmonary embolization from the right atrium in patients with atrial fibrillation is real. (8) (12) (45) However the incidence is quite low, even in the patient with an enlarged right atrium. Small pulmonary emboli may be relatively innocuous in a patient with adequate cardiac and pulmonary function. (45) In a patient with atrial fibrillation whether or not congestive heart failure is present, the pulmonary circulation is relatively engorged and the rate of blood flow is decreased as demonstrated by abnormal circulation times and pulmonary artery pressures. An embolus in such a situation has considerably greater potentialities for producing serious consequences.

Ultimately the decision as to whether or not conversion of the patient should be attempted is the decision of the individual physician. He is the one who knows or should know all of the ramifications of the particular case he is handling. However, a few of the major factors which influence this decision can be enumerated. The criteria as listed by Beckwith et al are generally acceptable. (7) These are the criteria which suggest that conversion of atrial fibrillation should be attempted:

(1) Patients with a history of embolic episodes

(2) Patients with refractory congestive heart failure not adequately controlled with digitalis, salt restriction and mercurial diuretics

(3) Patients with recently acquired atrial fibrillation which persists

(4) Patients without other evidence of heart disease who

give a history of embolic episodes and have heart failure and/or cardiac enlargement.

If one does not wish, or is unable, to attempt conversion of a patient to normal sinus rhythm, other courses are available which may be of help in removing some of the dangers associated with this arrhythmia. (7) (8) (12) (43) If the decision to attempt conversion of the patient to normal sinus rhythm is made, what agents are available?

THERAPY OF ATRIAL FIBRILLATION

Since the fortuitous discovery of quinine as an antifibrillatory agent, there has been little improvement in the therapy of atrial fibrillation. The only developments of consequence have been the introduction of quinidine sulfate, the dextroisomer of quinine in oral and parenteral form, and possibly the development of procaine amide. Other agents have shown some promise, but none of these have been accepted widely on a clinical basis. (46 - 51)

At the present time quinidine sulfate or gluconate are the drugs of choice in attempting conversion of fibrillating patients to normal sinus rhythm.

The therapeutic and toxic effects of quinidine appear to be related to plasma concentrations. (52) (53) Various dosage schedules are used in attempting to convert patients to normal sinus rhythm. The important factor seems to be the concentration of quinidine achieved in the myocardium. The myocardial concentration is a function of many factors, one of the more important being the rate of administration of the drug. Sokolow (53) states that peak plasma levels occur after

administration in two hours and that the incremental increase in blood levels becomes progressively less after four or five doses. This observation indicates that the total amount of quinidine is not as important as the number of hours over which the drug is given and also the size of the individual dose. If conversion does not occur with moderate blood levels, forcing the levels higher with increased doses is rarely successful and there is a risk of serious toxicity. (36) (53) (54)

The toxicity of quinidine is manifest in a number of ways; not necessarily related to dosage. Adverse reactions to quinidine may occur as muscular weakness, gastro-intestinal upset, vertigo, frequent ventricular ectopic beats, or ventricular tachycardia. (7) (55) Other reactions which may be seen are hemolytic anemia, (56) ventricular flutter, (59) and ventricular fibrillation with Stokes-Adams Syndrome.(59) Some of the deleterious effects of quinidine are primarily extensions of its pharmacologic action. They include a greater than 20 mm. drop in diastolic blood pressure and a widening of the Q R S and Q T intervals of the electrocardiogram. (55) A deleterious effect of myocardial efficiency due to intravenous quinidine gluconate has been demonstrated. (54) (59) This effect consisted of a 50 per cent reduction in stroke volume and a 27 per cent decrease in coronary artery flow per beat. Efficiency measured as Kg/M of left ventricular work per cc. of exygen fell to 45 per cent of normal. It is also reported that this drug may aggravate cardiac failure. (36)

If it were known why quinidine is superior to other drugs in the treatment of atrial fibrillation, it might be possible to improve upon it. That it has certain effects on atrial muscle is well known.

It elevates the threshold of electrical stimulation, slows the speed of excitation over the myocardium, and reduces conductivity at all rates of stimulation. (5) Stated in other words, quinidine prolongs conduction in the atrium, depresses myocardial excitability and prolongs the effective refractory period of myocardial tissue. (55) While the preceeding discussion does not include all of the known alterations of cardiac physiology induced by quinidine, these are the usual parameters within which new drugs are evaluated.

If the present laboratory methods for the evaluation of antifibrillatory drugs were valid, then quinidine should be no more effective clinically than other agents which produce the same experimental results.

It is pertinent to review briefly the currently available laboratory procedures utilized in the study of drugs intended for therapeutic use in atrial fibrillation. The relative refractory period of the myocardium may be measured using isolated rabbit atria stimulated electrically at various frequencies. (60-62) The electrical threshold current required to provoke abnormal beats can be obtained in a dog or cat with an open chest. (63-65) Using these preparations, an ill defined parameter termed nach flimmern may also be measured. Here, data is recorded on the amount of current required to provoke cardiac arrhythmias which persist for a few seconds beyond the time of electrical stimulation. After a baseline is established, the drug is infused and the preparation is restimulated; this is in essence the measurement of the prophylactic effect of the drug being tested. Atrial flutter or atrial fibrillation can be produced in dogs by a variety of techniques. Each is thought to illustrate one of the theories of the genesis of atrial fibrillation: -

crush by forceps of the intercaval bridge and a portion of the atrial appendage (the establishment of an infarct around which a "circus movement" may progress); - the subepicardial injection of the alkaloid aconitine (thereby provoking a single ectopic focus); - topical application of the cholinergic drug, Mecholyl, at and proximal to the sino-auricular node (multiple ectopic foci). (3) (5) (66) These experimental procedures have been vigorously utilized by pharmacologists since 1921, and yet no new effective drug for atrial fibrillation has been discovered.

A convincing argument for abandoning all procedures presently available for the study of antifibrillatory drugs was reported by Dick and McCawley in 1955. (54) They found that methantheline bromide (Banthine) had greater potency than quinidine in prolonging the relative refractory period and in elevating the electical and nach flimmern thresholds. Moreover it required a smaller dosage of methantheline than quinidine to convert atrial fibrillation established in dogs by all the maneuvers previously described. Yet when given trial in patients with chronic atrial fibrillation at twice the effective dose of quinidine, methantheline was unable to convert a single patient's arrhythmia to normal sinus rhythm. This consistent discrepancy between laboratory and clinical findings makes obvious the inadequacy of present experimental procedures and the need for a more valid method of evaluating antifibrillatory drugs.

When using laboratory methods we are dealing with normal tissue which has been altered in a specific manner. In the patient with atrial fibrillation, however, a pathological condition is present, the genesis of which is unknown. All that is known is that quinidine is the most effective agent available for restoring a normal situation. If its effectiveness in

this regard is not measured by present laboratory methods, how then can it be measured?

Our objective in the studies reported in this thesis is to utilize the major electrocardiographic alteration produced by large doses of quinidine as a basis for evaluating other drugs. We propose to do this by an infusion of quinidine gluconate into intact, healthy, anesthetized dogs and recording nearly continuously the electrocardiographic changes produced. The electrocardiographic changes produced by other chemical substances are to be compared with those of quinidine.

The following assumptions are made:

1. quinidine's action is directly on the myocardium and is not secondary to some other site,
2. the electrocardiogram records the resultant, at least, of forces acting on the heart during each phase of their action,
3. the electrical forces are a reflection of biochemical changes basic to myocardial depolarization and repolarization,
4. the elctrocardiographic changes observed with quinidine at large doses would also occur at small clinically useful dosage if more precise measurements could be made.

It is recognized that the following limitation is inherent in this line of reasoning. Presuppose that some such electrocardiographic correlation, as the broadening of the Q R S interval provoked by quinidine, were accepted as indicating effectiveness in atrial fibrillation. This criterion might reveal a new antifibrillatory drug having the same

mechanism of action as quinidine but would certainly overlook any drug having therapeutic merit in atrial fibrillation, but having a different mode of action than quinidine.

METHODS AND MATERIALS

These studies were performed using adult mongrel dogs in apparent good health. The dogs were anesthetized with 35 mg/Kg of pentobarbital sodium administered intraperitoneally.

Drugs were injected at a constant rate for each dog through a catheter placed in a femoral vein cut down. Rate of injections were controlled by one of three methods; a Murphy drip, a constant perfusion pump; or by single injections every minute through a three way stopcock. In the latter method, interval flow of saline was utilized in order to prevent clotting in the catheter.

The animals were shaved in appropriate areas over the legs and chest for placement of standard electrocardiographic leads. Two simultaneous electrocardiograms were recorded; as lead II and a chest lead placed over the point of maximal impulse. Once control values had been obtained, infusion of the drug was initiated. A ten centimeter segment of record was obtained, every minute for analysis. The styluses were kept in position of constant recording even though the paper was not moving. In this way, if any arrhythmia or significant change in heart rate occurred, it would be noticed immediately by merely looking at and listening to the styluses and a permanent record could be obtained.

Since quinidine and other drugs in this series may, in large doses, cause death by respiratory center depression and arrest, the animals were observed closely for this effect. In paired control studies, however, it was found that the electrocardiographic changes associated with quinidine toxicity were not altered when animals were intubated with an orotracheal airway and respirations supported by means of positive pressure with supplemental oxygen. Furthermore the data abstracted from the recordings was taken prior to the appearance of toxicity great enough to cause respiratory depression.

The various time intervals of the electrocardiogram were measured with the aid of fine calipers and a magnifying glass. A paper speed of 50 mm/sec was utilized to make interpretation easier. The Q R S, P R, and Q T time intervals were measured according to standard procedure. The vertical deflection on the recording was standardized so that a one centimeter deflection represented one millivolt.

All of the animals were administered the drug being tested to the point of lethal toxicity. A minimum of five dogs were used for each experiment.

An integration of Bazett's constant, as described by Lepeschkin,* was utilized in correcting electrocardiographic components for change in heart rate.

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*Lepeschkin, E., Modern Electrocardiography, Vol. I, 1st ed. The Williams and Wilkins Company, Baltimore, 1951.

RESULTS

Quinidine gluconate was administered to fifteen dogs, the perfusion rate varying in different experiments between 0.37 and 5.0 mg/Kg/min.

The data presented in Figure I represents average values for five dogs in which the rate of perfusion was 1 mg/Kg/min.

It should be immediately apparent from inspection of this graph that the Q R S and Q T intervals are prolonged by administration of quinidine. This tends to confirm reports in the literature to this effect. (2) (4) (5) It is also obvious that the Q R S interval is prolonged to a greater extent than the Q T interval. At a total dosage of 60 mg/Kg the Q R S time is doubled, while the Q T interval is only 30 per cent greater than the preinfusion value. The time required for ventricular depolarization was measured and is recorded in Figure I as the q R interval: or ventricular activation time. By inspection, it is seen that this factor is prolonged by quinidine to nearly the same extent as the Q R S interval of which it is a component. The corrected Q T interval, designated as Q T c and the (QT-QRS)c were determined according to Bazette's formula in order to correct changes occurring in these factors as a result of changes in heart rate. It can be seen that the Q T c shows less change than the Q T. Furthermore the (QT-QRS)c points out the fact that the prolongation of the Q T c is due entirely to prolongation of the Q R S. At 60 mg/Kg the qR is 75 per cent greater than the initial value and since the qR is a component of the Q R S, which is prolonged 100 per cent, it is seen that the qR is responsible

for 72 per cent of the increase in Q R S interval.

Figure II demonstrates a prolongation of the qR interval which is of the same magnitude as that seen with quinidine. It should be noted that the dosage required for this effect is only half of that which is required for quinidine. This correlates well with clinical data available for allocryptopine with respect to effective dosage. (48) (49) The prolongation of the Q T c at this dosage, however, is not significantly different than that which occurs with quinidine.

The most striking change noted in Figure III is the considerable increase in the Q T interval. When this is corrected with Bazette's formula, however, the Q T c demonstrates rather insignificant prolongation. The qR is onlymoderately prolonged, and then at relatively high dosage. There is a difference of opinion regarding the effectiveness of this drug clinically in chronic atrial fibrillation. (2) (67) (68) (69) Furthermore the mechanism of action of procaine amide probably differs from that of quinidine as indicated by Etrati (57) in his report of a case of quinidine induced ventricular flutter treated successfully with procaine amide.

Atabrine (Figure IV) demonstrates a rather variable effect. The qR interval is slightly prolonged initially, but then rapidly declines. At pre-lethal doses it begins to increase again, but never reaches the initial maximal prolongation. The Q T and Q T c follow essentially the same curve as the qR.

With Benadryl there is no effect on the qR interval. While the Q T is increased 72.5 per cent at 47.5 mg/Kg, the Q T c shows only a 35 per cent increase. At 60 mg/Kg there is a 100 per cent increase in the Q T interval and when this is corrected for heart rate the prolongation

is only 18 per cent. (Figure V)

As with Benadryl, methantheline shows no increase in the ventricular activation time (qR interval). At pre-lethal doses, the Q T is increased 52 per cent, but when this is corrected for heart rate the increase is reduced to 17.5 per cent.

In addition to studying agents which had been used in clinical trials on patients with atrial fibrillation, a total of twenty other drugs were surveyed using this experimental method. To our knowledge, from a survey of the literature, none of these twenty drugs had ever been subjected to clinical evaluation in the treatment of this arrhthymia.

In Table I it can be seen that SC-3920 and ajmaline both give significant changes in the qR interval of the electrocardiogram when compared with quinidine (Figure I). The dosage required is well below that of toxicity. At 76 per cent of the lethal dose, corycavine shows a 45 per cent increase in the ventricular activation time; with SC-3920 a 120 per cent increase at 50 - 60 per cent of fatal toxicity occurs. Ajmaline demonstrates a 220 per cent increase in time of ventricular depolarization at a 20 per cent lethal dosage.

Inspection of Tables II and III reveals no pertinent electrocardiographic alterations. It is noted that this correlates well with the data shown previously (Figures I, IV, V, and VI), and in clinical trials of the compounds to which most of these drugs are related (Table IV).

A total of five dogs were administered quinidine gluconate at a rate of 1 mg/Kg/min. Following the appearance of obvious toxicity as manifest by electrocardiographic changes, Na lactate in M/2 solution was given as rapidly as possible. The subsequent changes in the electro-

cardiograph are noted (Figure VII). These changes are representative of those occurring in the other four animals. The possibility that the electrocardiographic alterations were due to a hypervolemia has not been ruled out. The reason for using this agent was that the electrocardiographic alterations due to quinidine (Figure I) might be explained on the basis of a loss of sodium ions at a cellular level, or an increase of potassium ion. (71) (72) Another possibility is that lactate ion may supply added acetate radicals, (73) (74) essential for myocardial metabolism in the presence of the protoplasmic poison quinidine.

FIGURE I

Effects of Quinidine Gluconate on the

Electrocardiogram

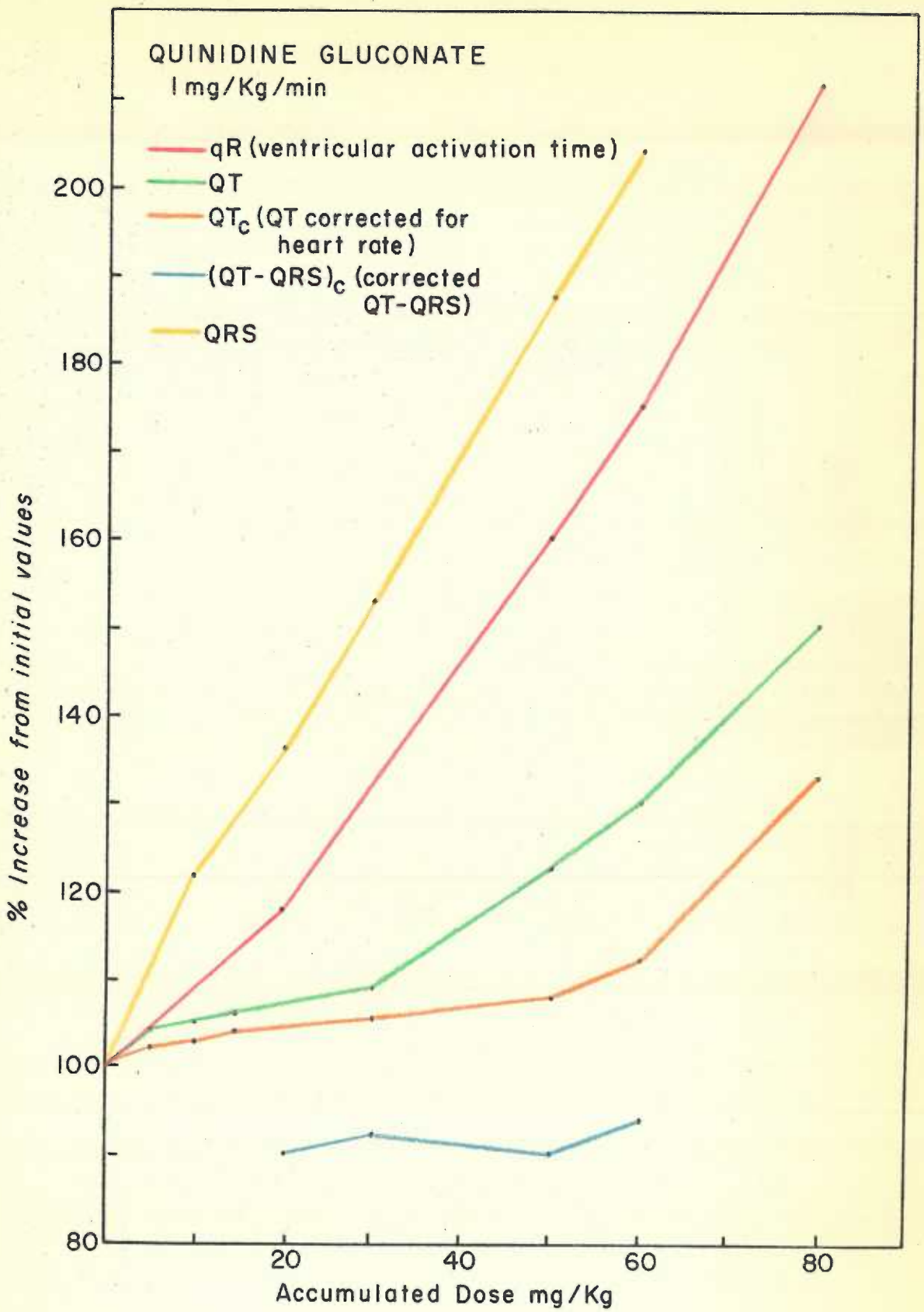

QUINIDINE GLUCONATE
1 mg/Kg/min
qR (ventricular activation time)
QT
QTc (QT corrected for heart rate)
(QT-QRS)c (corrected QT-QRS)
QRS
% Increase from initial values
200
180
160
140
120
100
80
20
40
60
80
Accumulated Dose mg/Kg

FIGURE II

Effects of Allocryptopine (alpha fagarine) on the Electrocardiogram

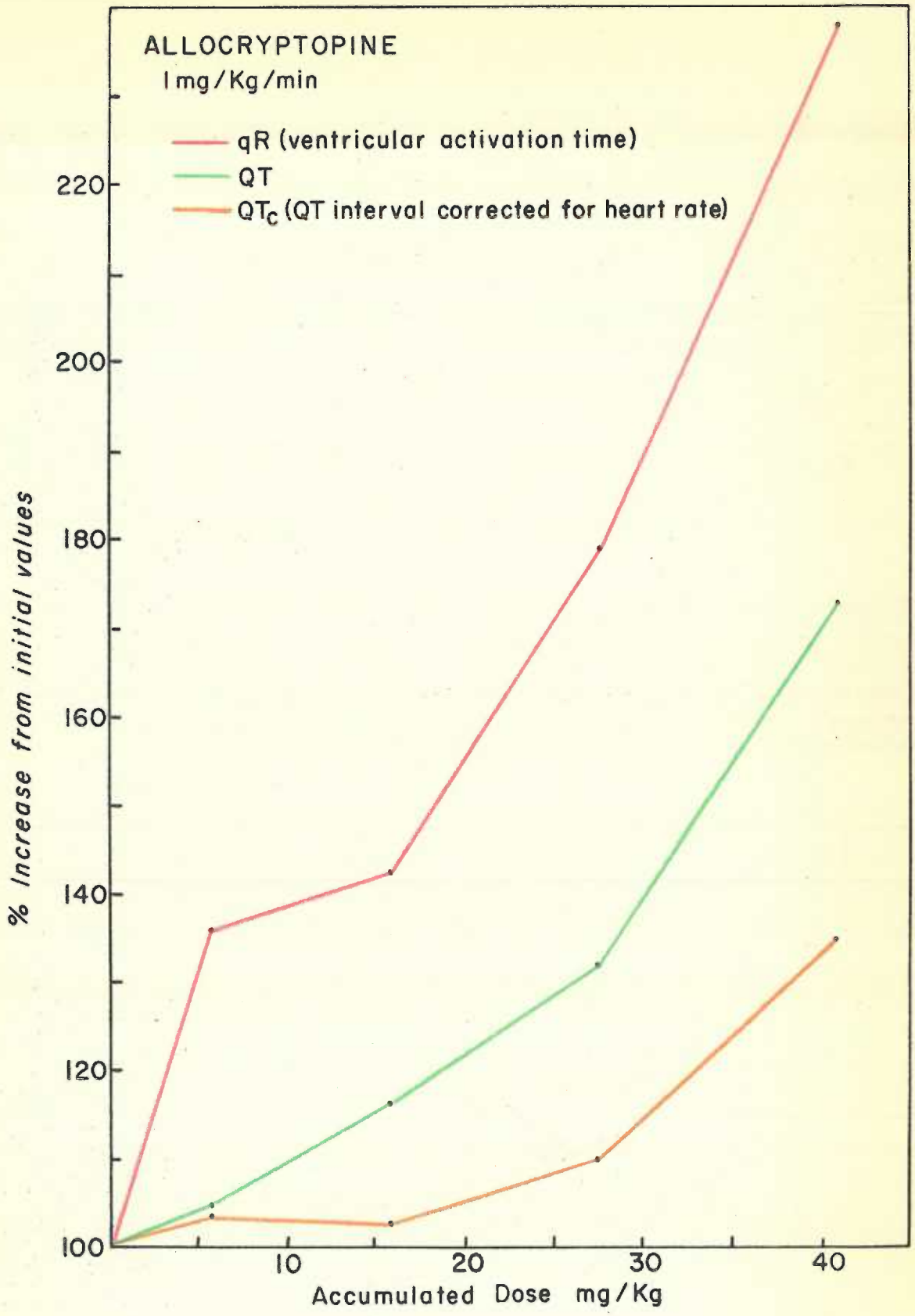

ALLOCRYPTOPINE
1 mg/Kg/min
qR (ventricular activation time)
QT
QTc (QT interval corrected for heart rate)
% Increase from initial values
100
120
140
160
180
200
220
10
20
30
40
Accumulated Dose mg/Kg

Figure III

Effects of Procaine Amide on

the Electrocardiogram

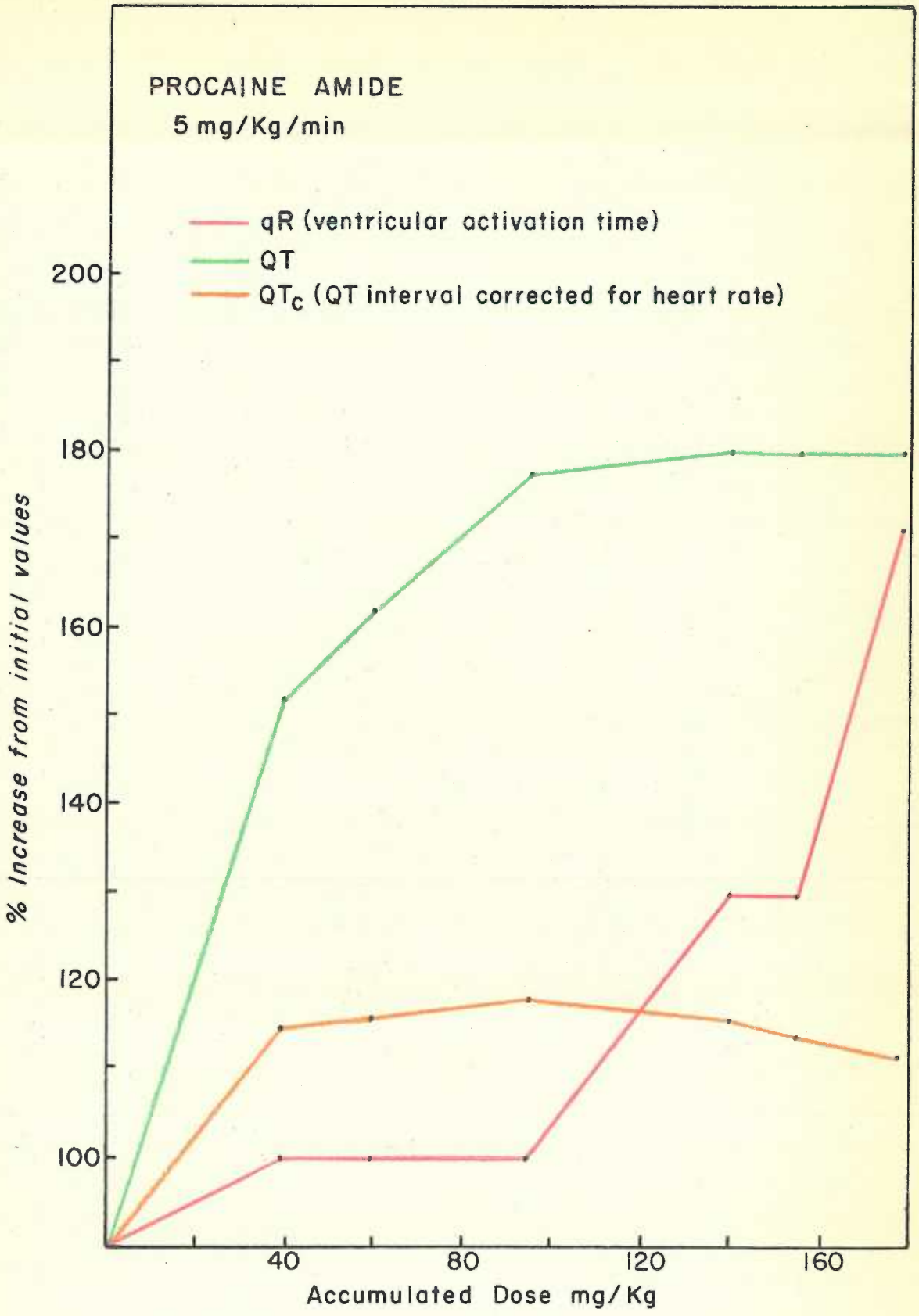

PROCAINE AMIDE
5 mg/Kg/min
qR (ventricular activation time)
QT
QTc (QT interval corrected for heart rate)
200
180
160
140
120
100
% Increase from initial values
40
80
120
160
Accumulated Dose mg/Kg

Figure IV

Effects of Atabrine Hydrochloride

on the Electrocardiogram

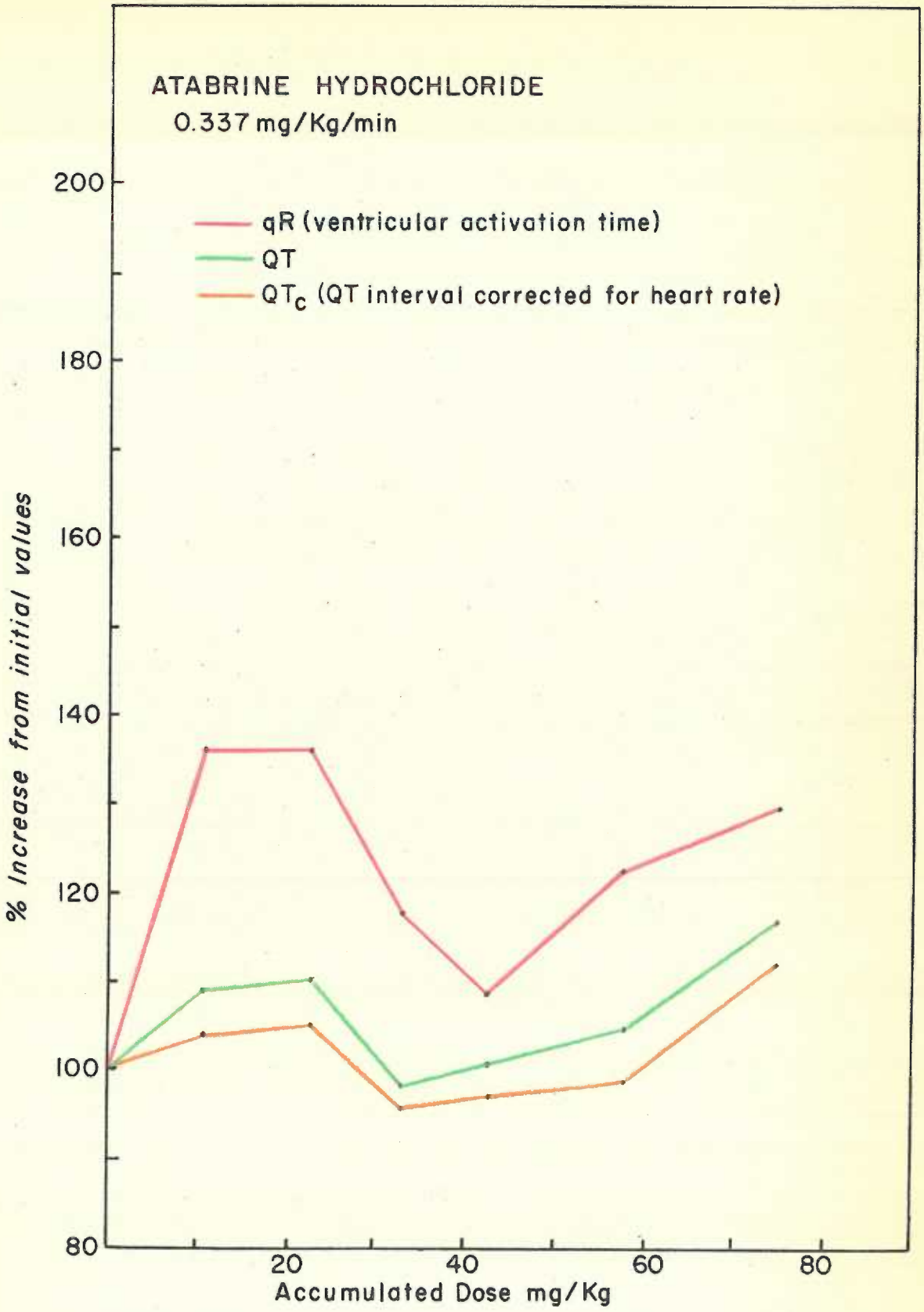

ATABRINE HYDROCHLORIDE
0.337 mg/Kg/min
qR (ventricular activation time)
QT
QTc (QT interval corrected for heart rate)
% Increase from initial values
200
180
160
140
120
100
80
20
40
60
80
Accumulated Dose mg/Kg

Figure V

Effects of Benadryl Hydrochloride

on the Electrocardiogram

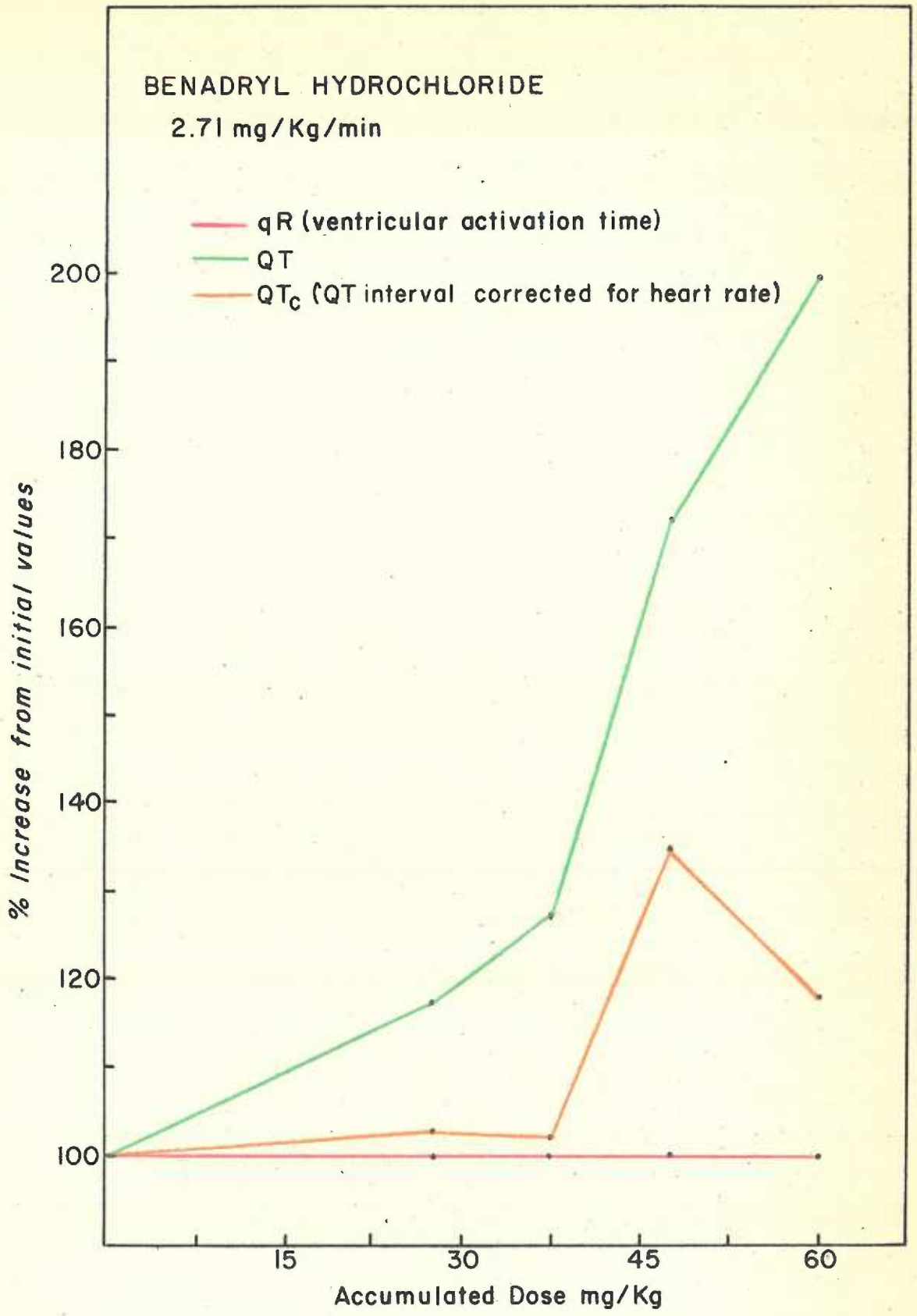

BENADRYL HYDROCHLORIDE
2.71 mg/Kg/min
qR (ventricular activation time)
QT
QTc (QT interval corrected for heart rate)
200
180
160
140
120
100
% Increase from initial values
15
30
45
60
Accumulated Dose mg/Kg

Figure VI

Effects of Benthine Bromide on

the Electrocardiogram

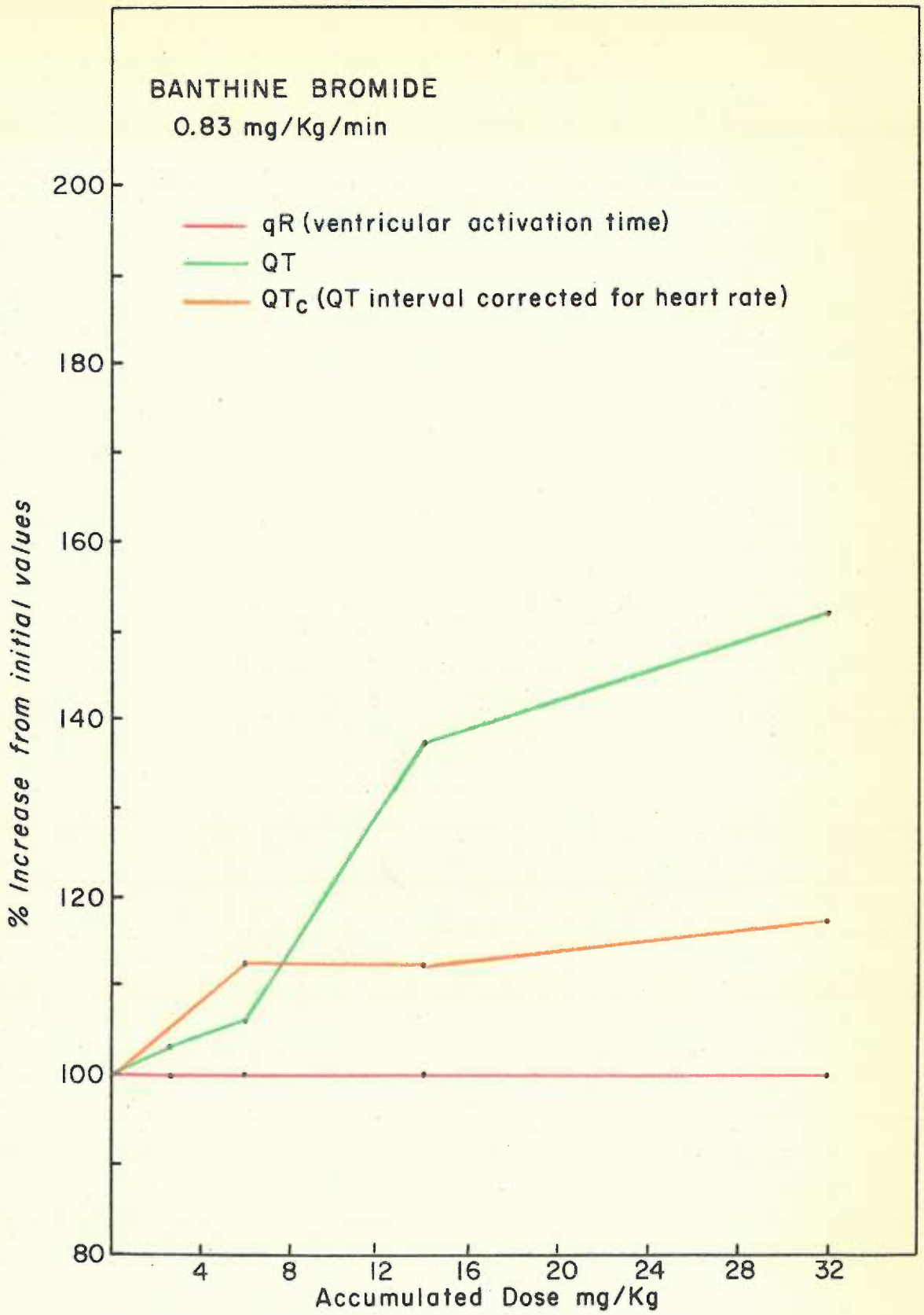
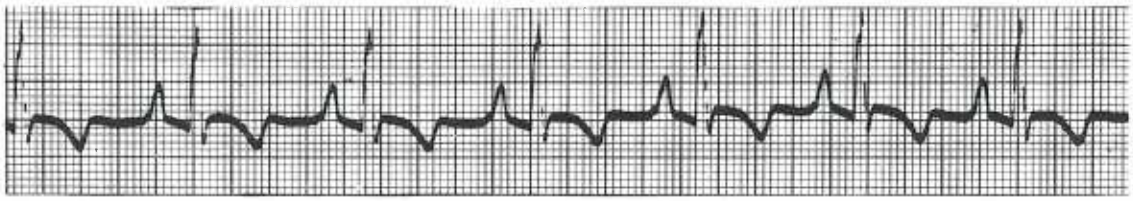

BANTHINE BROMIDE
0.83 mg/Kg/min
qR (ventricular activation time)
QT
QTc (QT interval corrected for heart rate)
% Increase from initial values
200
180
160
140
120
100
80
4
8
12
16
20
24
28
32
Accumulated Dose mg/Kg

Figure VII

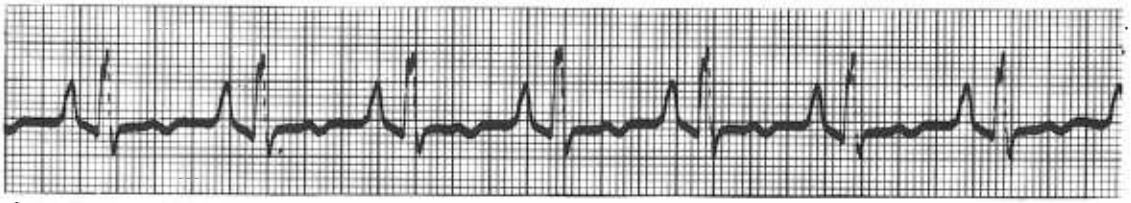
Effect of M/2 Sodium Lactate on Electro-cardiographic Changes Due to Quinidine Toxicity

Fig. 7 EFFECT OF M/2 Na LACTATE ON EKG CHANGES PRODUCED BY QUINIDINE TOXICITY

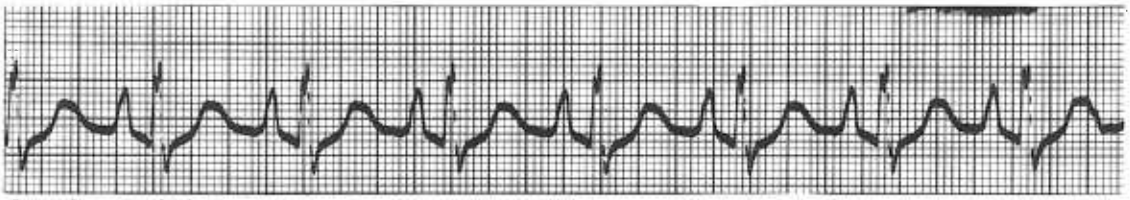
10 Kg dog 1mg/Kg/min of quinidine gluconate



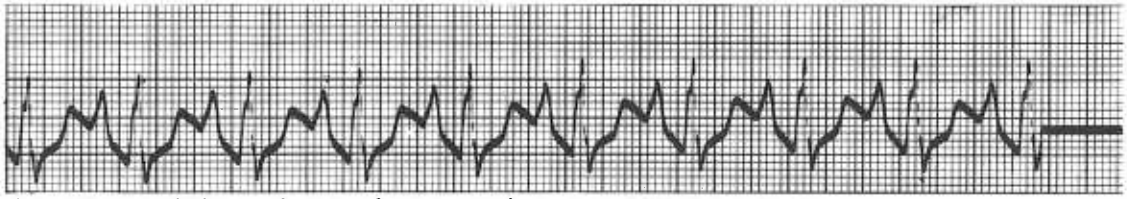
Control



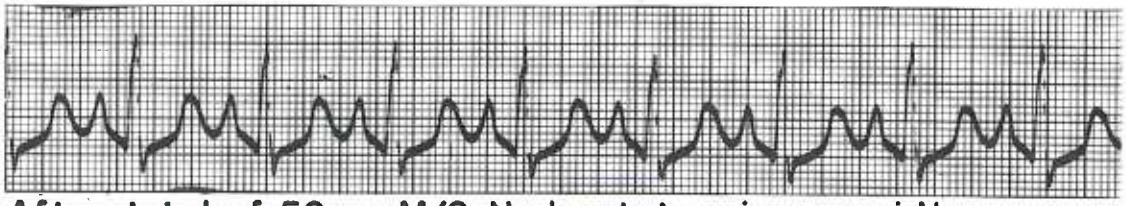
At 5mg/Kg



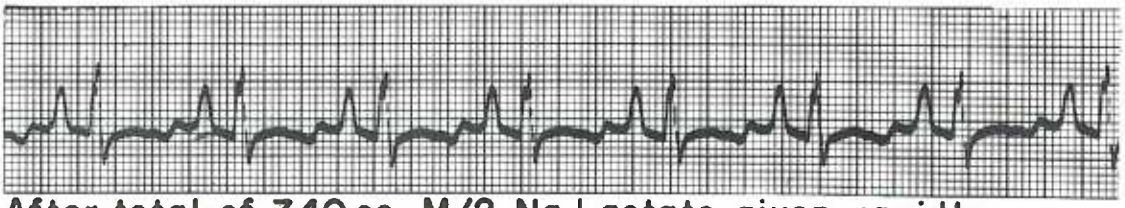
At 6mg/Kg



At 16mg/Kg last dose prior to Na Lactate



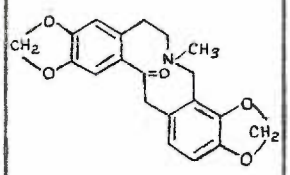
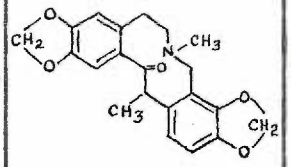
After total of 50cc M/2 Na Lactate given rapidly



After total of 340cc M/2 Na Lactate given rapidly

TABLE I

Compounds Related to Allocryptopine (alpha fagarine)

Name	Formula	Ventricular Activation Time	R-R Interval	P-R Interval	QTc	Dose
Protopine		+ 70% at 40 mg/Kg	tachy-cardia	+24% at 40 mg/Kg	No change	1.0mg/Kg/min. Lethal 45 mg/Kg
Corycavine		+45% at 25 mg/Kg	+43% at 25 mg/Kg	+60% at 25 mg/Kg	+30% at 25mg/Kg	1.0 mg/Kg/min. lethal 33 mg/Kg

Compounds Related to Procaine Amide

Name	Chemical Name	Ventricular Activation Time	R-R Interval	P-R Interval	QTc	Dose
	γ - isopropyl amino propyl) αα diphenyl acetamide SC-3920	+120% at 10 mg/Kg	-67%	+100%	+8%	1 mg/Kg/min. lethal 15-20 mg/Kg

Miscellaneous Derivatives

Name	Chemical Name	Ventricular Activation Time	R-R Interval	P-R Interval	QTc	Dose
	RO 2-7302/4	+68%	+100% at 50 mg/Kg	+115% at 50 mg/Kg	decre-ased	0.5 to 1.0 mg/Kg/min. lethal-50-80 mg/Kg
Ajmaline	$C_{20}H_{26}O_2N_2$ Yohimbine derivative from Rauwolfia	+40% at 0.9 mg/Kg +220% at 5 mg/Kg	tachy-cardia initially later +106%	+136% at 5 mg/Kg	Decre-ased	1 mg/Kg/min. lethal - 25 mg/Kg

TABLE II

Anti-malarial Drugs (Atabrine)

Name	Chemical Name	Ventricular Activation Time	R-R Interval	P-R Interval	QTc	Dose
Chloroquin	7-chloro-4 (4 diethyl-amino-1-methyl butyl-amino)quinoline SN-7618	No change	+45%	+31%	+60%	1 mg/Kg/min.
Amodia-quin	4-(7-chloro-4-quinolyl-amino) ∝ diethylamino-o-cresol SN-10,751	No change (bigeminy)	No change	No change	Not pro-longed	0.26-6.0 mg/Kg/min.
	4-(7-chloro-4-qinolyl amino) ∝ dibutyl amino-o-cresol SN 14,105	No change	+30% at 300 mg/	+45%	Not pro-longed	4.6-4.8 mg/Kg/min. lethal-384 mg/Kg
	4-(7-chloro-4-quinolyl-amino) ∝ -1-piperidyl-o-cresol SN 11,636	No change (bigeminy)	No change	No change	Not pro-	1.0 mg/Kg/min. lethal - 106 mg/Kg
	4-(7-chloro-4-quinolyl-amino) - ∝ -isobutyl amino) -o-cresol	No change (bigeminy)	No change	No change	Not pro-longed	0.7 mg/Kg/min. lethal 117-185 mg/Kg
		Compounds Related to Benadryl				
Ambodryl	p-bromo-dibenz-hydryl dimethyl ethyl amine A-890	No change	+70% at 30 mg/Kg	No change	Not pro-longed	2.5-10 mg/Kg/min., lethal 38 mg/Kg
Linadryl	dibenzhydryl ethyl morpholine A-446	No change	+47% at 100 mg/Kg	No change	Not pro-longed	1.2-2.8 mg/Kg/min., lethal 167 mg/Kg
	dibenzhydryl di-ethyl ethylamine S-45	No change	+ 40% at 25 mg/Kg	Shortened	Not pro-longed	0.2-2 mg/Kg/min., lethal-28.8 mg/Kg

TABLE III

Anticholinergic Drugs (Banthine)

Name	Chemical Name	Ventricular Activation Time	R-R Interval	P-R Interval	QTc	Dose
Piptal	N ethyl-3-piperidyl benzilate methobromide JB-323	No change	+60% at 50 mg/Kg	+10% increase	No prolongation	1.2 mg/Kg/min. lethal - 55 mg/Kg
Dactil	N-ethyl-3-piperidyl diphenyl acetate JB-305	+35% at 90 mg/Kg	+94% at 90 mg/Kg	No change	No prolongation	0.76 mg/Kg/min. lethal - 92 mg/Kg
	N-methly-3-piperidyl benzilate methobromide JB-340	+7%	-7%	+94% at 44 mg/Kg	shortens	1 mg/Kg.min. lethal - 45-50 mg/Kg
	dibenzhydryl dimethyl ethylamine methobromide S-135 S-92	No change	-84%	shortens	shortens	0.2-2.5 mg/Kg/min. lethal - 25 mg/Kg
		Sympathomimetics				
	N-(2-p-methoxyphenyl) isopropyl arterenol JB-245	decreased	tachycardia	+36%	shortens	0.83 mg/Kg/min. lethal - 100 mg/Kg
	JB-246	No change	tachycardia	no change	shortens	2.2 mg/Kg/min. lethal - 45 mg/Kg
	JB-251	8% increase	tachycardia	no change	+13%	1.14 mg/Kg/min. lethal - 95 mg/Kg

TABLE IV

Comparative Therapeutic Effectiveness of Drugs

in "Chronic" Atrial Fibrillation in Man

(Duration 2 months to 6 years)

Drug	Number of Patients	Number Converted	References
Allocryptopine HCL (Alpha Fagarine)	6	5	48, 49
Atabrine HCL	13	0	46, 47, 50
Banthine Bromide	8	0	51
Benadryl HCL	7	2	51
Pronestyl HCL	27	4	67 - 70
Quinidine Sulfate	10	6	51

DISCUSSION

It has been customary to attribute all of the virtues of quinidine, as an antifibrillatory agent, to its ability to prolong the refractory period of the myocardium and all of its shortcomings to the slowing of myocardial conduction.

The classic circus movement theory was proposed by Lewis and Drury (75-77) in 1925. At that time they postulated that quinidine abolished atrial fibrillation by increasing the refractoriness of atrial muscle, thereby decreasing the "excitable gap" which was responsible for the perpetuation of the arrhythmia. When quinidine fails to convert atrial fibrillation, the explanation offered is that the slowing of myocardial conduction widens the "excitable gap" and the circus movement is perpetuated.

Investigators, dissatisfied with the circus movement theory, propose as a basis for the genesis of atrial fibrillation, the theories of a single ectopic focus or multiple ectopic foci. (5) (78) Quinidine abolishes an arrhythmia produced by ectopic foci through decreasing the rate of discharge from these abnormal pacemakers. This is thought to occur as a result of increasing the refractoriness of the muscle about the ectopic focus. Prolongation of the refractory period of heart muscle denotes a decrease in electrical excitability, therefore quinidine abolishes atrial fibrillation by prolonging the myocardial refractory period and at the same time suppressing the activity of abnormal pacemakers with subsequent restoration of normal rhythm.

That property of quinidine which slows myocardial conduction has been looked upon as deleterious because it may cause the production

of an intraventricular block (5) (9) with subsequent ventricular tachycardia or ventricular fibrillation. Others have stated that the broadened Q R S interval must be attributed to quinidine's having produced a bundle branch block (79) (80)

In bundle branch block conduction proximal to the point of block may be normal, but circumvention of the blocked area by the impulse requires a greater length of time than normal and depolarization is prolonged. Whether this prolongation involves the qR or the Rs will be determined by the bundle involved and the lead used in obtaining the record.

In the experiments reported here, quinidine prolongs both the initial and terminal portions of the Q R S interval. It does this by slowing the rate of myocardial conduction. If the widening of the Q R S interval induced by quinidine were due to a bundle branch block characteristic changes, as a result of the abnormal conduction, would be seen.

The vectorcardiogram is useful to confirm this point. In the manner described previously, quinidine gluconate was infused at a rate of 1 mg/Kg/min. Leads I and II were used as input for the X and Y plates of the oscilloscope. The frontal plane Q R S loop vectorcardiogram was obtained and it was found that quinidine even at 60 mg/Kg changed neither the shape nor the direction of the long axis of the loop.

Since there was no alteration in the contour of the electrocardiogram, quinidine cannot have altered the time sequence of ventricular depolarization;(81) there was no bundle branch block.

The validity of any theory is established when its com-

ponent parts withstand critical laboratory experiments. When, however, the theoretical mode of action of quinidine is applied to other drugs there is a poor correlation between laboratory and clinical results. Drugs having a greater potency than quinidine in prolonging the "effective" refractory period of isolated rabbit atria are not necessarily effective in clinical atrial fibrillation. (51)

In contrast, the results described in this thesis indicate that there is a correlation between a drug's ability to slow myocardial conduction and its effectiveness in clinical atrial fibrillation. Quinidine (Figure I) and allocryptopine (Figure II) prolong the Q R S interval (slow myocardial conduction) and both are effective in arresting chronic atrial fibrillation in patients. Pronestyl (Figure III), Atabrine (Figure IV), and Benadryl (Figure V) do not significantly retard myocardial conduction and they are ineffective in chronic atrial fibrillation, although they may be effective in paroxysmal atrial fibrillation. Benthine (Figure VI) does not slow myocardial conduction at all and this drug is of no value in clinical atrial fibrillation.

Thus it is proposed that: Quinidine's effectiveness in chronic atrial fibrillation is based on its ability to retard the rate of myocardial conduction.

The rate of conduction can be measured directly by the use of microelectrodes applied to the heart. (82) This procedure was not adopted because of its inherent technical difficulties as well as producing an unphysiological state, and because it would have added nothing to this study that could not more readily and conveniently

be obtained by means of the standard electrocardiogram.

According to current electrocardiographic interpretation, the inscription of the Q R S is the electrical correlate of ventricular contraction. As such, the Q R S interval represents the time required for complete ventricular depolarization; and is therefore a measure of the time required for electrical conduction throughout the ventricles. I_n this work the measurement of the qR interval was used to determine the action of quinidine on myocardial conduction. The standards of the American Heart Association stipulate that the Q R S is to be measured as follows: its initiation is the beginning of the downward deflection representing the Q wave, or, in its absence, the inflection beginning the R wave. The termination of the Q R S occurs when the S wave returns to the isoelectric line. Difficulties are encountered when these criteria are applied in interpreting the action of quinidine on the Q R S interval.

Quinidine causes an increase in the magnitude of the S wave. Due to inertia of the writing lever, tissue impedance and other factors not related to quinidine's action, the upward deflection of the S wave may be delayed. In leads which do not demonstrate an S wave a change in the "S-T" junction may occur as a result of the action of quinidine. Thus alterations in the terminal portion of the Q R S may not represent ventricular depolarization but rather artifacts. Furthermore the significance of the intrinsicoid deflection is not well understood. (83)

Because of these difficulties associated with interpretation of the effects of quinidine on the total Q R S interval, it was felt

that more accurate, and just as significant, measurements could be obtained utilizing the qR interval.

The action of quinidine in retarding myocardial conduction, thereby prolonging the qR and Q R S intervals, provides a correlation between electrical and mechanical cardiac activity. In discussing the mechanism of action of quinidine it is pertinent to inquire into the cellular changes generating the forces which permit inscription of the Q R S by means of the electrocardiograph.

It is well documented that the electrocardiogram records the sum of the dipole activities occurring in the myocardium at a given moment. (71) (82-86) Less well known are the factores responsible for these bioelectric potentials. It is generally accepted that the sodium potassium cationic gradients are the source of the electromotive forces produced. (71) (87) (88) Nachmansohn (87) (88) has summarized the major factors known concerning bioelectric membrane potentials. He states that the movements occurring during electrical activity (depolarization) are with the gradients. In other words, initiation of activity by sodium ion transfer across the myocardial membrane requires very little energy. The alteration of membrane permeability which precedes the influx of sodium ion in all conducting tissue is a function of acetylcholine, and the focus of action of this ester is within the conducting membrane (89) (90) The acetylcholine which provokes initiation of sodium ion influx is rapidly destroyed by cholinesterase and it is known that conduction along a membrane cannot be dissociated from this enzyme. After acetylcholine is hydrolyzed the choline is reacetylated by choline acetylase in the presence of adenosinetriphosphate which provides

the energy for this reaction. When cholinesterase activity is blocked with physostigmine, impulse propagation along the membrane is blocked. It has been demonstrated that quinine and presumably also quinidine can inhibit plasma cholinesterase, approaching physostigmine in its magnitude of activity. (55) Clinically, the symptoms of myasthenia gravis are aggravated by quinine. (91)

From this preceding discussion it is seen that acetylcholine initiates sodium ion transfer and consequently is one of the major factors in the alteration of the cationic gradient necessary for production of the bioelectric potential. Also, for conduction to occur normally, cholinesterase is essential, as are choline acetylase, adenosinetriphosphate, and possibly other factors not yet recognized.

The effect of the altered sodium potassium cationic gradient on the electrocardiogram was studied in detail by Lenzi and Caniggia (71) These investigators found that when the extracellular sodium ion concentration was increased the following changes occurred:

1. The T wave was prolonged and became diphasic with a negative terminal phase.
2. The Q R S interval was decreased as was the voltage of the R wave.
3. The isoelectric S-T segment became markedly prolonged.

When the extracellular potassium was increased, these changes were observed:

1. The T waves initially became abrupt and of higher voltage.
2. The Q R S interval was markedly increased.
3. The isoelectric S-T segment became shorter and eventually depressed.

The changes observed may be explained in the following manner. With the onset of depolarization there is an influx of sodium ions and an egress of potassium. When the extracellular sodium ion concentration was increased, the influx of sodium ion and the efflux of potassium was augmented by the change in the gradient; this results in the more rapid depolarization. During repolarization the reverse occurs. When the extracellular potassium ion concentration is increased the gradient is reversed and depolarization is prolonged. These findings fit well into the theory of muscle contraction as proposed by Szent Györgi(92)

In reviewing the results obtained qith quinidine (Figure I) and allocryptopine (Figure II), it is seen that the significant changes in the electrocardiogram are those involving ventricular depolarization.

Using the criteria established by Lenzi and Caniggia, these alterations may be explained by one of the following:

1. Increased potassium ion concentration in the proximity of the cell imeding efflux of potassium and thereby sloving depolarization.

2. Decreased extracellular sodium ion concentration, since if potassium is to leave the cell sodium must be available to replace it.

3. Impaded movement of sodium or potassium ion across the membrane by some mechanism other than alteration in extracellular ion concentrations.

That the first two possibilities may occur is unlikely, for relatively large changes in ionic concentrations would be required to produce the effect seen. The third possibility is more amenable to explanation and will just as readily account for the electro-

cardiographic alterations. Furthermore the action of quinidine would more likely be on the ionic exchange mechanism rather than on increasing or decreasing absolute concentrations of ions. Nachmansohn postulates the following steps in the acetylcholine - cholinesterase cycle:

1. Acetylcholine in the resting phase is bound and inactive, probably associated with a protein.
2. Excitation causes release of acetylcholine from its complex.
3. The free acetylcholine acts on a specific receptor, presumably a protein.
4. The action on the receptor causes a change in ionic permeability(possibly due to rearranging protein configuration).
5. The free ester is hydrolyzed by free acetylcholinesterase.
6. The hydrolysis of acetylcholine permits the receptor to return to its resting position, re-establishing the barrier to rapid ionic exchange.

From our results the action of quinidine is most readily explained by virtue of its effect on depolarization, for when the effect of quinidine on repolarization is corrected for heart rate, it is insignificant. The most readily available explanation for the prolongation of depolarization would be the impedance of sodium ion transfer. From the postulates advanced by Nachmansohn the site of action of quinidine could be either in impeding release of acetylcholine from its resting state, or in altering the receptor protein so that it does not become so readily permeable to sodium ion. Since very little energy is required for sodium to pass the membrane barrier, any interfer-

ence at this level should not necessarily block transmission of the ion completely, and the effect would be that of prolonging rather than preventing depolarization. The fact that the bizarre electrocardiographic changes associated with severe quinidine toxicity are partially alleviated by large doses of M/2 sodium lactate (Figure VII), given intravenously, coincides with this hypothesis.

It was mentioned that quinidine may be a potent cholinesterase inhibitor and the question arises as to whether this is the basis for its electrocardiographic effect. If this were the case, the changes should be just the opposite of those observed, for in such a situation acetylcholine would not be destroyed, the receptor protein would not return to its resting position and there would be no barrier to ionic exchange.

If the efficacy of an antifibrillatory agent is related to its ability to prolong ventricular activation time, we would conclude that allocryptopine (Figure II) is a more effective drug on a weight to weight basis than is quinidine (Figure I); this has been confirmed in clinical trial. (48) (49) Further inspection of the experimental results and Table IV tends to confirm the correlation between prolongation or ventricular activation and antifibrillatory potency, for it is seen that those agents which are ineffective clinically fail to prolong the qR interval to any significant degree.

Tables I, II, and III represent the screening of twenty compounds. Most of these are related chemically to drugs which have

received clinical trial in this arrythmia. As determined by our method only two of these drugs show promise as antifibrillatory agents.

It is apparent that there are many interesting questions yet to be answered. The locus of action of quinidine has been suggested but by no means worked out. While we have not definitely elucidated the fundamental action of quinidine in correcting cardiac arrhythmias it is felt that the method described gives us, as a basis for correlating the effectiveness of antifibrillatory agents, a factor which is directly related to the ability of quinidine to convert clinical atrial fibrillation to normal rhythm. We have approached as nearly as possible a least common denominator for the therapeutic effectiveness of quinidine and other antifibrillatory agents which would act in the same manner.

SUMMARY AND CONCLUSIONS

A review of the pertinent literature indicated that patients with atrial fibrillation will be improved significantly following conversion to normal sinus rhythm. Following restoration at normal rhythm, there should be an increase in cardiac output, elimination of functional mitral insufficiency, a return of physiologic response to vagal activity and a decrease in embolic complications.

Therapy, using quinidine, may be disappointing and even dangerous according to some investigators. Careful control of dosage, using the electrocardiograph and quinidine blood levels, affords only incomplete protection.

Previous experience indicates that there is a poor correlation between the effectiveness of antifibrillatory drugs in experimental animals and the results of trial in patients with atrial fibrillation. These observations raise serious doubt that the mechansim of action of quinidine is related to a prolongation of the myocardial refractory period. Since the experimentally induced atrial fibrillation in dogs is presumed to illustrate circus movement or ectopic foci, the failure to correlate experimental with clinical effectiveness of drugs studied in these animals raises doubt as to the value of these theories when applied to the pathogenesis of atrial fibrillation.

1. The effect of toxic doses of quinidine on the electrocardiogram was studied in detail and the interpretation of these effects was in accordance with the generally accepted explanation. It was observed that prolongation of the Q T interval is due to a lengthening of the Q R S. When the Q T interval was corrected for heart rate its

entire increase could be attributed to the prolonged Q R S.

2. Because of the intrinsic difficulties in measuring the Q R S, the qR interval was utilized in determining the effect of quinidine on the myocardium. Bundle branch block, due to quinidine, did not occur with the dosages used in these experiments, therefore the prolongation of the q R interval was due to generalized slowing. There was found to be a direct correlation between a drug's ability to prolong the qR interval and its effectiveness in chronic atrial fibrillation.

3. A new theory is proposed that: the effectiveness of quinidine as an antifibrillatory agent is related to its abiltiy to prolong myocardial conduction. This is diametrically opposed to current concepts on the mechanism of action of quinidine in atrial fibrillation. Currently slowing of myocardial conduction is believed to represent a deleterious effect of quinidine and prolongation of the refractory period, the therapeutic action.

4. A possible site for the action of quinidine in prolonging depolarization is suggested.

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