QUINIDINE IN DISORDERS OF THE HEART

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Preface

THIS monograph on the use of quinidine in the treatment of disorders of the heart is intended primarily as a guide for the general practitioner. Since emphasis is placed on a way of thinking about these problems and planning for them, it is my hope that both medical students and specialists in cardiology may find informative reading in it. Many of the observations and the methods advocated here are in complete agreement with those of others. Accordingly, the writings and views of others receive considerable attention. This is not, however, a review of the literature in the usual sense, but a personal account of knowledge based on experience with successes and failures, reading, and reflection in relation to this subject during a period of about twenty-five years; in the teaching of laboratory and clinical pharmacology to medical students; pharmacologic and clinical research; the care of several thousand cardiac patients in the hospital, clinic, and private practice; postgraduate medical courses; and lectures to groups and societies of medical practitioners of widely different interests, skills, and experience.

Observation has led me to the belief that only a small part of the potentialities of quinidine in disorders of cardiac rhythm is put to effective use, although these disorders are among the very common problems encountered in medical practice. The chief reason for this is the use of rigid stock methods rather than technics that are custom-built to suit the particular individual. What is often wanting is sufficient familiarity with the mechanism of the disordered rhythm and with the pharmacology of quinidine. These data, if properly integrated, lend flexibility to any method with

which treatment is started, and provide not only for rational beginnings, but also for rational changes in procedure indicated by the initial results.

In the presentation of the material, I have tried to pursue a fairly uniform plan: to define the particular physiologic mechanism to which quinidine is to be applied; to crystallize the precise therapeutic objective; to explain the particular action of quinidine on which dependence is being placed; to point out the sources of danger that may apply in special situations; to outline the doses with which treatment is begun with the intervals between doses, methods of adjustment and guides to adjustment in dosage; to discuss the complicating actions of the drug which may confuse the issue in a particular case; and to describe the toxic effects of quinidine and methods for their control. Particular emphasis is placed on the rationale of the practices that are advocated. An attempt has been made to clear certain matters by the account of case histories. Special sections have been included which deal with general principles applicable to the use of quinidine in all cases. Details of clinical diagnosis and prognosis have been kept at a minimum, and presented only where they seemed to be of some importance for a better insight into the problems of treatment.

In the account of the mechanisms of various disorders of rhythm and of the mode of action of quinidine, I have adopted formulations which are most commonly accepted. Many points on mechanisms are unsettled and involve controversial issues. I have utilized the concept of the circus movement in the explanation of some of the problems, although there is considerable evidence to the effect that the mechanism in a particular disorder may not be a circus movement, but multiple foci of excitation with asynchronism in the contraction of muscle blocks. I have

made use of the conventional concepts of the S-A node, A-V node, and conduction systems, although evidence has appeared which suggests that none of these applies to the human heart. As further knowledge is added and our understanding of mechanisms is better crystallized, some of the statements may need revision. The decision to do this was made in the interest of avoiding confusion and maintaining the length of the theoretical discussions within limits consistent with the text as a whole.

A selected bibliography, arranged chronologically, is appended. It is a limited one, and does not even include all of the best papers, but it should serve the purpose of directing the reader's attention to some of the more important literature bearing on special points mentioned in the text.

There is no doubt of the fact that there are particular patients in whom a disorder of rhythm cannot be controlled by quinidine. The considerations listed above help to discover who these are, and help to distinguish therapeutic failures due to the drug from those due to its improper application. The importance of judgment based on experience in the use of quinidine should not be underestimated, but in examining my own experiences in which a threatened defeat or disaster seemed to have been averted, I find that the responsibility for the result was usually to be ascribed to the application of one or another of the foregoing considerations. If I have described them sufficiently clearly, I shall have reason to hope that this monograph may succeed in enhancing the power of quinidine as an instrument of therapy in disorders of the heart.

To Professor McKeen Cattell I wish to express my appreciation of the generous number of hours he took from a crowded schedule to review the manuscript and especially to scrutinize the statements relating to basic

pharmacology and physiology. His comments have proved invaluable. It is a particular pleasure to express my gratitude to Dr. Theodore Greiner, one of our Research Assistants in Clinical Pharmacology during the tenure of a National Institute of Health Fellowship. He brought the fresh perspective of a recent medical graduate to bear on a critical examination of an early draft and rendered substantial aid in rephrasing sections to insure their intended meaning. To Dr. Leon J. Warsaw I am in debt for valuable help in the final revision of the manuscript, the reading of proof, and for the major work in the preparation of the index. I am also greatly obligated to Dr. Nathaniel T. Kwit and Dr. Walter Modell for their liberal assistance in the review of the more practical sections, the assembling and checking of bibliography, and the reading of proof. To my daughter Naomi I am deeply indebted for the arduous task of taking and typing dictation of the greater part of the preliminary draft of the text.

New York HARRY GOLD, M.D.

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in Disorders of the Heart

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Indications

WHILE the cinchona bark contains more than twenty alkaloids, the general discussions are based on quinidine alone. This is done so because quinidine is the most important member of the group in the treatment of disorders of the heart and the largest part of the clinical literature on the cardiac actions of this group of compounds relates to quinidine. All doses of quinidine, unless otherwise stated, will refer to quinidine sulfate, since this is the salt most commonly prescribed. It is well to bear in mind, however, that several of the cinchona alkaloids closely related to quinidine have received attention in regard to their actions on the heart and circulation, and are of importance in special cases in which quinidine itself cannot be used. These exert cardiac actions that are similar to quinidine, but there are significant quantitative differences, and there are some indications of qualitative differences. A more detailed discussion of the other compounds and the conditions under which they may be called upon is found in a later section.

Disorders of cardiac rhythm constitute the only indications for the use of quinidine in disturbances of the heart. It has no primary place in the treatment of cardiac pain or failure. There are some conditions in which quinidine prevents or abolishes cardiac pain or failure, but such results are due neither to direct dilatation of the coronary arteries nor direct action on the force of contraction of cardiac

muscle. When they occur, they are the indirect result of the prevention or abolition of one or another disorder of cardiac rhythm which in some individuals gives rise either to cardiac pain or failure.

The following is a list of the disorders of cardiac rhythm in which quinidine is effective:

1. Premature contractions or extrasystoles (auricular, nodal, ventricular)
2. Paroxysmal auricular tachycardia
3. Nodal tachycardia
4. Auricular flutter
5. Auricular fibrillation
6. Ventricular tachycardia
7. Ventricular fibrillation

It is perhaps well to call attention to the fact that not all of these disorders of rhythm always require treatment. For example, there are many patients in whom premature contractions are discovered in a routine examination, the patient being unaware of their presence. Many do just as well, and some better, when allowed to continue with these ectopic beats which are in themselves harmless. There is also the fact that some of these disorders of rhythm may be treated in other ways and by means of other drugs. The circumstances in the particular cases will determine the decision.

The disorders of cardiac rhythm present themselves in two general forms of therapeutic problems. The one concerns the patient in the midst of an ectopic rhythm which needs to be terminated and a normal rhythm restored. The other concerns the patient with a normal rhythm but with a history of repeated paroxysms of ectopic rhythm which need to be prevented. These two problems are often presented by the same patient.

Although a course of quinidine therapy to abolish premature contractions is usually carried out with the patient up and about, the restoration of a normal rhythm with quinidine in the case of the other disorders should rarely be attempted unless the patient is under close supervision and at rest. On the other hand, the prevention of attacks or recurrences is usually a problem of treatment in the ambulant patient.

I mentioned the fact that the indications for quinidine in cardiac disorders are the ectopic rhythms, and that these are among the very common problems encountered in medical practice. That about 25 per cent of an average cardiac population presents problems of disordered rhythm is probably a fair estimate. The number of these cases does not, however, satisfactorily reflect the importance of a drug which is effective in controlling them. A large proportion of patients with abnormal rhythm have a condition which is of no great consequence, affecting neither their ability to carry on nor their longevity. In many patients, the condition produces no symptoms and the disorder of rhythm may first be discovered during an examination for some other purpose. In fact, the onset of some patients' troubles often dates back to the time when the disorder of rhythm was called to their attention. There is, however, a sizable group in which the abnormal rhythm takes on the aspect of a serious disease. Among these, depending on the kind of disorder of rhythm, the type of patient, the condition of the heart, the following may result: cardiac neurosis, panic, palpitation, cough, attacks of syncope, cardiac pain, pulmonary edema, congestive failure, emboli, shock, and death.

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Therapeutic Actions

IT IS probably only one basic action of quinidine which accounts for the large number of therapeutic applications of the drug in disorders of cardiac rhythm, namely, increase in refractoriness of the various cardiac structures. However, quinidine exerts many actions on the heart, the circulation, and extracardiac structures. It is necessary to bear this in mind in order to comprehend the wide variety of reactions which are observed in the numerous conditions in which it is used. The utility of the drug depends on the wide differential in doses necessary to affect different structures and to produce the various changes. It would hardly prove a useful drug in ventricular tachycardia, for example, if the same dose which suppresses the rapid ectopic pacemaker in the ventricle also suppressed the normal pacemaker of the sino-auricular node or stimulated the vomiting center. The fact that the rapid ectopic focus in the ventricle is relatively more sensitive to quinidine than the normal sinus node or the vomiting center accounts for the large number of cases in which ventricular tachycardia is uneventfully controlled. But patients differ, and there are some in which these differentials are either eliminated or reversed. Thus, undue sensitivity of the gastrointestinal tract is responsible for one of the limitations in the therapeutic usefulness of the drug, and undue sensitivity of the normal sinus pacemaker, approximating that of the ectopic ventricular pacemaker, accounts for one of

the serious hazards of the drug, namely, complete cardiac standstill with doses which are required to abolish the ventricular tachycardia. Many similar examples could be cited.

Familiarity with the basic actions of quinidine on the heart and other structures is very helpful in the therapeutic use of this drug for disorders of cardiac rhythm. While in the large proportion of cases the desired therapeutic action is dominant, and such simple dosage plans as will be described lead to the uneventful control of the cardiac disorder, there are many others in whom undesirable actions both on the heart and on extracardiac structures, so-called side-actions, intrude. An understanding of these is of material assistance in charting the course of therapy, especially in the case of the more difficult problems. Although there are many gaps in our knowledge of the basic actions of quinidine, enough information has been obtained from animal experiments and direct observations on man to afford a basis for understanding most of the common patterns of response during the therapeutic use of this drug. The more important effects and those most likely to be encountered in the routine use of quinidine are here listed.

1. Quinidine prolongs the refractory time of heart muscle. This has been determined in various ways. The essence of one experimental method consists of applying electrical stimuli at varying intervals of time to the rhythmically beating heart. When these stimuli fall far enough from the previous beat, they evoke a response; when they fall too near the previous beat, they fail to evoke a response. The longest time-interval between the normal beat and the extra stimulus which fails to call forth a response is one way of measuring the refractory time. The refractory time varies considerably from animal to animal, and with the rate of the beat. The refractory

period of the auricle has been found to vary under different conditions, from less than 0.1 to about 0.2 second. Quinidine may lengthen this interval between one beat of the heart and its readiness to respond to another stimulus by as much as 100 per cent. In another method similar information has been obtained by the effect of the drug on the peak rhythm of the isolated rabbit auricle. For example, without the drug the auricle might respond to rhythmic stimulation at rates up to 250 a minute, and at a rate of 260, there may be failures of response to some of the stimuli; quinidine might reduce the peak rate to 200 a minute with failures of response at rates above that. The extent of the lowering of the peak rate has been found to depend on the dose of the drug. This method has been utilized as a means of comparing the potency of various agents possessing a quinidine-like action.

2. Quinidine slows conduction in the heart muscle. The speed of conduction is determined experimentally in the intact heart by applying a stimulus to the heart, and recording the response simultaneously from two points on the heart. From the record of the difference in time between the responses at the two points and the distance between the two points, the speed of conduction is calculated. This also varies considerably with the rate and condition of the heart. The speed of conduction in the auricle has been found to vary from about 500 to 2000 mm. per second, under various conditions.

This action of quinidine is also observed directly in man by the use of the electrocardiogram: slowing of the circus movement in auricular fibrillation and flutter, prolongation of intraventricular conduction (prolonged QRS time), and prolongation of A-V conduction (prolonged P-R interval).

3. Quinidine exerts an antifibrillary action on the heart.

This has been observed in animals and directly in man. There is the observation that auricular fibrillation may be promptly terminated by a dose of quinidine, and ventricular fibrillation prevented. In animal experiments, a tetanizing current of sufficient intensity applied to the heart sends it into fibrillation. After quinidine, the heart is more resistant to the tetanizing current and now the intensity of the stimulus must be increased to send the heart into fibrillation. This effect is usually explained by the action of quinidine in prolonging refractory time, although some other type of action may be involved since there are substances which shorten refractory time and yet act to prevent fibrillation.

4. Quinidine depresses the excitability of heart muscle. In animal experiments, a threshold stimulus which evokes a response is no longer effective after the muscle has been exposed to quinidine.

5. Quinidine acts directly on the heart to depress rhythmic function. In animal experiments, it may slow the sinus rhythm after atropine, which indicates that it is a direct action and not one due to vagal stimulation. Also, high blood concentrations reached by very slow intravenous infusions, sufficient to block the vagus, may result in slowing of the heart. Sinus slowing is sometimes seen in humans. Quinidine also slows the rate of ectopic pacemakers, as in ventricular tachycardia in animals and man, and in larger doses may completely suppress the rhythmic activity of the entire heart.

6. Quinidine slows the electrical systole of the heart. This is detected by the prolongation of the Q-T interval of the electrocardiogram. The change may result from slowing of conduction or prolongation of the recovery phase. This effect may be observed in animals and man. What part it plays in the therapeutic or toxic actions of quinidine is not known.