Treatment of HEART DISEASE

BRAMS

Treatment of
HEART DISEASE

By WILLIAM A. BRAMS, M.S., M.D., Ph.D.

Associate Professor of Medicine, Northwestern University Medical School, and Attending Physician, Michael Reese Hospital, Chicago

ILLUSTRATED

Philadelphia & London

W. B. SAUNDERS COMPANY

1948

MADE IN U. S. A.

PRESS OF
W. B. SAUNDERS COMPANY
PHILADELPHIA

PREFACE

Many years of clinical teaching, private practice and consultation work have convinced me that the general practitioner and the medical student feel a great need for a systematic and practical guide in the treatment of heart disease. This book is an attempt to provide such a guide, based on my own experience in private and hospital practice.

No attempt has been made to include descriptions of additional methods favorably reported by others. It is conceded that such a plan necessarily limits the scope of the book, but it also permits greater clarity and conciseness, features which are of importance in a book of this kind.

It may be argued that the plan is somewhat dogmatic and that no single method of treatment is suitable for all patients. There is no denying that any plan of treatment may require modification because of atypical clinical features, occurrence of complications, or variations in response to therapy. Any attempt to provide suggestions for all possible contingencies would result in a mass of detail which could only prove confusing. It is my opinion that it is pedagogically more sound to familiarize the physician with the pharmacologic properties of the various drugs used in the treatment of heart disease so that he can himself institute such modifications in therapy as may be necessary. This is particularly important in determining some of the causes for failure of therapeutic response and in distinguishing untoward or toxic effects of the drugs from clinical manifestations of the disease process itself. It is for these reasons that a comprehensive survey of the pharmacologic properties of the more important drugs employed in the treatment of heart disease is included.

No attempt has been made to preface each discussion of treatment with a more or less complete summary of etiologic, symptomatic and diagnostic features of the disease to be treated since this book is concerned primarily with therapy. It is felt that clinical descriptions of the various diseases are described adequately in the several textbooks available on heart disease. It

must be presumed that the patient has been studied carefully and that at least a tentative diagnosis has been made before the physician is ready to plan a course of treatment. On the other hand, I consider it profitable to devote some space to pertinent discussion of important coexisting conditions, such as diabetes, thyrotoxicosis, pregnancy, etc., as they relate to the treatment of heart disease.

It will be noted that a great amount of space is devoted to treatment of congestive heart failure. I feel that the subject is of paramount importance since the majority of patients with almost any form of organic heart disease ultimately develop congestive heart failure. It is surely no exaggeration to state that ability to treat congestive heart failure is an essential prerequisite for successful treatment of heart disease. Furthermore, many of the therapeutic measures employed in congestive heart failure are also useful in management of other cardiac disturbances. Repetition is eliminated and space is thus conserved by referring to descriptions of such therapeutic measures in the chapter dealing with treatment of congestive heart failure.

Finally, I wish to acknowledge my indebtedness to Dr. L. N. Katz for many valuable suggestions that are incorporated throughout the text. Thanks are due to Dr. M. D. Allweiss and other colleagues for additional suggestions and to Miss Paula Bennett who rendered invaluable service in preparation of the manuscript.

WILLIAM A. BRAMS

May, 1948

CONTENTS

CHAPTER 1

CHAPTER 2

CHAPTER 3

CHAPTER 4

I

THE PHARMACOLOGIC ACTION OF DRUGS USED IN THE TREATMENT OF HEART DISEASE

The suggestions in this book will prove adequate for the great majority of patients with heart disease. Variations in the clinical picture will be encountered from time to time and modifications in treatment will be necessary to meet such contingencies. The scope of this book does not permit the undertaking of detailed discussions of all possible variations in treatment. It is believed, however, that familiarity with the pharmacologic properties of the remedies employed in heart failure will aid the physician to vary his treatment sufficiently to meet all needs. It is for this reason that a comprehensive survey of current concepts regarding such pharmacologic effects is included.

DIGITALIS AND ITS ALLIES

DIGITALIS

Digitalis, long the sovereign remedy for the treatment of heart failure, was introduced into medical practice by William Withering[1] in 1785. The plant had been used for many years in the treatment of various other conditions but Withering recognized its great value in dropsy and noted many of its beneficial effects on the heart. Another century passed before its pharmacologic properties and therapeutic indications were studied adequately. Much of the best work has been done in the past twenty-five years.

The standard preparations of digitalis in use today are derived from the leaves of digitalis purpurea. Many other preparations are available, including those derived from other varieties of digitalis or from sources having a digitalis-like action. The effects of all these differ from standard preparations only in minor respects:

none are superior and many are inferior. The best clinical results are usually obtained with standard preparations of digitalis purpurea.

The complete therapeutic action of digitalis is due to several glycosides, the most important being digitoxin.[64] The interaction of the various glycosides on one another is said to be of importance.

Biological assay of preparations derived from the whole leaf is a reliable method by which quantitative activity of digitalis is determined. Gravimetric estimations of various glycosides are also satisfactory.

The Pharmacologic Effects of Digitalis

Digitalis, applied locally, is irritant and will cause pain if injected subcutaneously or intramuscularly. The major therapeutic effects are those exerted on the heart, the most important being *slowing of the heart rate* and *increase in the strength of myocardial contraction*. These, and other effects to be described later, are much more apparent with therapeutic doses in heart failure than in the normal heart.[2, 3, 4] Toxic manifestations with small doses of digitalis are more likely to occur if the myocardium is severely damaged. This increased sensitivity of the failing heart to the beneficial and toxic effects of therapeutic doses of digitalis is of great practical importance.

Increased Myocardial Contraction.—The strength of myocardial contraction is increased by digitalis,[22, 27, 58] the effect being more marked on the ventricles than on the auricles. Isolated strips of myocardium, when exposed to solutions of oubain or digitoxin in dilutions corresponding to those occurring in man during treatment, are capable of much greater force of contraction to fixed stimuli than under control conditions. These experiments show that there is a direct action on the myocardium.[37] Observations on the whole heart of animals and indirect studies in man support the contention that digitalis increases the strength of myocardial contraction by direct action on the muscle tissue.[10, 21, 30, 60, 64, 65] Stronger myocardial contraction results in more complete emptying of the ventricles with an increase in the stroke and minute volume output of the heart.[80] This improvement in pump action is augmented by slowing of the heart rate to optimum levels and by elimination of the many feeble and comparatively useless contractions of the ventricle if auricular fibrillation is

present. All these factors will be discussed more fully later but the net result is reduction of venous stagnation and improvement of arterial circulation. Circulation in the coronary arteries is also improved, resulting in better myocardial nutrition and increased capacity for work. It should be mentioned that such beneficial actions do not occur shortly after administration of digitalis unless large doses are injected intravenously, or some quickly acting preparation like strophanthin is used. Hence digitalis in small dosage is no quick acting cardiac stimulant for use in emergencies.

Slowing of the Heart Rate.—Slowing of the heart rate by digitalis constitutes one of its major therapeutic effects. Slowing is the result of two mechanisms: stimulation of the vagus apparatus and direct depression of auriculoventricular conduction tissue. Both mechanisms frequently play a part, especially when larger doses of digitalis are employed.

Stimulation of the vagus apparatus usually occurs before appreciable heart block is induced. There is good evidence that the vagus endings and the carotid sinus are the chief elements responsible for vagal slowing of the heart rate rather than the vagus center as formerly believed.[36] Vagus stimulation depresses the sinus node thus slowing the rate of impulse liberation from the normal cardiac pacemaker. It is possible that other factors also play a part but these require further study. Larger doses of digitalis depress conduction from auricles to ventricles, first by way of the vagus and later by direct depression of the conducting tissues. The vagal element may be eliminated by atropine but direct depression of the conducting tissue is not so influenced. Hence atropine is of little value as an antidote for severe heart block induced by excessive doses of digitalis. Slowing of the ventricular rate by induction of heart block is best seen in auricular fibrillation with rapid ventricular rate. Here the sinus node is not operative and digitalis affects the auricular mechanism of auricular fibrillation only slightly or not at all. The ventricles are slowed as a result of heart block between the auricles and ventricles so that the rate of the latter is reduced to normal or below.

Slowing of the ventricular rate to optimum levels is of great therapeutic value. The ventricles are "rested" since diastole is prolonged. Longer diastole permits more time for venous return into the heart with consequent reduction of venous congestion.

More time during diastole also permits better coronary flow within the myocardium. The passage of blood from auricles to ventricles is also facilitated by longer diastole of the ventricles. The result is better nourishment of the myocardium and a more efficient heart. Better filling of the heart results in a stronger myocardial contraction: i.e., greater output into the arterial system and better nourishment of all tissues. Slowing of the ventricular rate in auricular fibrillation produces such striking beneficial effects that a number of observers believed this to be the chief if not the sole therapeutic accomplishment of digitalis. This conception is not entirely true since improvement has also been observed with little or no slowing of the ventricular rate, particularly when the rhythm is regular.[96] Slowing of the heart rate, whether induced by depression of the sinus node or of the conducting tissues, must not be permitted to result in a rate below norml, i.e., below 70 to 80 beats per minute. Abnormally slow rates result in very long diastole which may lead to excessive filling of the heart: an effect which is undesirable when the heart is severely damaged by disease.

Other Properties of Digitalis

Increase of Myocardial Excitability.—Larger doses of digitalis may increase excitability of the specific conducting tissues,[16] particularly of the ventricles. This may result in the production of extrasystoles or paroxysmal, ectopic rhythms. The familiar coupling of a normal beat with an extrasystole, the well-known pulsus bigeminus, has long been recognized as a sign of digitalis toxicity which serves as a warning that digitalis must be reduced or stopped. Extrasystoles alone, when not caused by digitalis, should not be considered a contraindication to the use of digitalis, since such irregularities may be due to poor myocardial blood supply and may disappear when coronary circulation is improved by digitalis. Digitalis may induce other manifestations of increased myocardial excitability, such as paroxysmal tachycardia, auricular flutter, auricular fibrillation, the very dangerous ventricular tachycardia, or fatal ventricular fibrillation.

Effects on Blood Vessels.—*Blood pressure* can be elevated in experimental animals by digitalis. This is due to increased cardiac output and direct constrictive action on the walls of the arteries. Therapeutic doses in man do not affect blood pressure except as a

result of improved cardiac action. Such a rise in blood pressure is not excessive and is an expression of improvement of the circulation. In any event, *neither the presence of hypertension nor the fear of inducing it should serve as a contraindication to the use of digitalis if heart failure is present.*

Much attention has been paid recently to the effects of digitalis on the *coronary arteries* and in angina pectoris. Strips of coronary artery immersed in solutions of digitoxin may be seen to contract.[24] Experiments on animals show variable results[70] depending on the dosage used, technic employed, condition of the nervous connections of the heart, cardiac rate and the functional state of the heart. A conspicuous change is seldom observed in the coronary arteries of the intact dog or cat, and such changes, when seen, have not been sufficiently correlated with the possible effects of the anesthetic,[30] dosage of digitalis and changes induced by the experimental technic. It is difficult to compare results obtained in animal experiments under such conditions with those seen in clinical therapeutics. The comparison is particularly difficult when we note that other observers failed to see unfavorable effects in experimental animals when doses were used which were comparable to those employed in clinical practice.[10, 23, 77, 85] It has been said that digitalis may induce anginal attacks in susceptible patients[40] but clinical evidence concerning this point is conflicting.[41, 61] Careful observations on large groups of patients with angina pectoris receiving digitalis, even in large doses, failed to disclose greater incidence of pain than in a similar group receiving only placebos.[68] It would seem to be unwise to withhold digitalis in cardiac failure in patients who also have angina pectoris.

Absorption and Fixation of Digitalis

All digitalis glycosides are absorbed from the gastro-intestinal tract, but not at the same rate. Some are absorbed so slowly after oral administration that a considerable portion is destroyed in the gastro-intestinal tract.[10] Similar variability in absorption and some degree of destruction locally are believed to occur after subcutaneous or intramuscular injection.[10] This, if true, would make these routes much inferior to intravenous injection if parenteral administration is necessary.

A so-called *full therapeutic dose* of digitalis, given orally, produces electrocardiographic changes in two to four hours. Such changes

consist of depression of the S-T segment or depression or inversion of the T wave. The maximum degree of such changes is apparent in six to twenty-four hours and persists for about twenty-four hours, although some change may occasionally be present for as long as three weeks.[6, 12, 13, 14] Such electrocardiographic changes are accepted as evidence of the onset of digitalis action on the heart but it has not yet been determined how much of these effects is due to therapeutic and how much to toxic action. It is generally believed that therapeutic effects after such a full dose of digitalis occur at about the same time as the electrocardiographic changes. *Small or moderate doses* of digitalis produce therapeutic effects after a longer interval; three to seven days or more, depending on the amount given and on the capacity of the heart to respond.

It has been estimated that from 0.1 to 0.13 gm. (1½ to 2 grains) of digitalis or its equivalent is used up or destroyed daily in the human body, once the therapeutic effects are attained.[28, 29] This is the average *maintenance dose* under these conditions but no fixed rules can be established since elimination, destruction and response to digitalis vary. Elimination or destruction of a given dose of digitalis is greatest shortly after administration or when larger amounts are already present in the body.[49, 54, 55] This may explain why some patients tolerate larger maintenance doses while well digitalized and why cumulative symptoms sometimes appear when smaller doses are given over a long period of time. Several instances of digitalis toxicity have come to my attention in which patients were receiving from 0.065 to 0.1 gm. (1 to 1½ grains) of digitalis daily for some time. The foregoing estimations of the amount of digitalis used up or destroyed daily in the body were made with digitalis which is 25 to 30 per cent less potent per unit of weight than the digitalis which is dispensed at present. Hence a reduction in the average daily maintenance dose to about 65 mg. (1 grain) would seem justifiable.[84]

A special virtue of digitalis is its prolonged effect on the heart and the fact that addiction or tolerance is not known to occur. This does not relieve the physician from the responsibility of watching the patient closely while digitalis is being given since some of the variable factors mentioned before may become operative without much warning.

Severe congestion of the liver or gastro-intestinal tract may

delay absorption of digitalis from the digestive tract when given orally. This permits greater destruction of digitalis in the intestinal tract.[30] The destroyed portion may be sufficiently great to render the remainder therapeutically inadequate. The practical significance of this mechanism has been overlooked too often as shown by the fact that intravenous or rectal administration is sometimes effective when the oral route fails.[6]

Intravenous injection of digitalis or its allies, while not recommended for routine use, is sometimes imperative when rapid action is desirable or when the oral or rectal routes are impracticable. Neither digitalis nor strophanthin is modified or fixed in the blood or lungs after intravenous injection. About 10 per cent of the injected amount is fixed to the heart, the remainder being taken up by the skeletal muscles, liver, kidneys and other tissues.[30] The portion not fixed to the heart does not become available subsequently for fixation to the myocardium, the one exception being the portion of digitalis which enters edema fluid or serous effusions. Digitalis held by such fluid is released during diuresis and may become fixed to the heart as described later.

Rectal instillation or the use of suppositories containing digitalis[56, 66] is frequently useful when the oral route is unsatisfactory and parenteral administration is not considered desirable. Part of the digitalis absorbed from the rectum reaches the inferior vena cava and heart directly without encountering venous stagnation in the liver or bowel. The rectal dose is the same or somewhat greater than that used orally and the entire day's requirement can be given as a single dose. Absorption is fairly rapid and the results are good if a cleansing enema is given just before rectal administration.

Toxic Manifestations

Toxic manifestations are due generally to overdosage or to cumulative effect after prolonged medication. The cause in either case is quantitative excess in the body. Toxicity may also be observed after average or small doses when the diseased myocardium is abnormally sensitive to digitalis.[79]

It is generally believed that cumulation is due to gradual increment of digitalis in the heart muscle to toxic levels when the daily intake exceeds the quantity used up. Large doses of digitalis or cumulative increment in the heart muscle, while producing