CARDIAC ARRHYTHMIAS

DIAGNOSIS AND TREATMENT

second edition

edited by

NOBLE O. FOWLER M.D.

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With 11 contributors

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DRUG DOSAGE

The authors and publisher have exerted every effort to ensure that drug selection and dosage set forth in this text are in accord with current recommendations and practice at the time of publication. However, in view of ongoing research, changes in government regulations, and the constant flow of information relating to drug therapy and drug reactions, the reader is urged to check the package insert for each drug for any change in indications and dosage and for added warnings and precautions. This is particularly important when the recommended agent is a new and/or infrequently employed drug.

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Foreword

Since the first edition of this book was published in 1970, significant new information has been developed which may be applied to the management of cardiac arrhythmias. While not many FDA-approved new drugs have appeared, certain important issues have become resolved. On the other hand, not only do some old questions remain unanswered, but a number of new questions have been posed.

Our understanding of the mechanism of action of antiarrhythmic drugs has been greatly improved. Despite this fact, the selection of antiarrhythmic agents is still largely empiric. Nevertheless, it is useful to remember that conduction within the ventricles is decreased by one group of antiarrhythmic agents (such as quinidine or procainamide) but is improved by another group (such as dilantin and lidocaine) (1). This information may be useful when an agent in one group is not effective in the management of a tachyarrhythmia. It would then appear to be more logical to use an agent from the other group.

Lidocaine, procainamide and other drugs given parenterally are very effective in the treatment of ventricular arrhythmias following acute cardiac infarction. However, it has become clear that the long-term management of ventricular premature beats is difficult, is often attended by drug-induced complications, and usually is of uncertain benefit. Most asymptomatic people with normal hearts probably should not receive drugs for management of premature cardiac contractions. When evaluated several weeks following myocardial infarction, patients who have premature ventricular contractions which exceed five per minute, are multifocal, or occur in salvos, appear to have an increased mortality rate during subsequent months. This same group of patients, however, usually has evidence of cardiac enlargement or left ventricular dysfunction. Controlled clinical trials are needed to determine whether or not antiarrhythmic drugs can reduce the prevalence of sudden death in such patients. It is unproven that coronary artery bypass surgery will be helpful in preventing fatal ventricular arrhythmias in this group of patients.

There have been significant advances in the surgical management of Wolff-Parkinson-White syndrome. Seely, Wallace and associates at Duke University have now treated over 30 patients successfully. Not only has the anatomy of AV nodal bypass tracts become more clearly defined, but also it now appears that effective surgical management is available for nearly all patients who fail to respond to drug management.

Coronary Care Unit observations indicate that a few patients with acute coronary insufficiency and associated ventricular tachyarrhythmias may not respond to drugs but may respond to coronary bypass surgery. An important issue with regard to the management of patients with acute myocardial infarction relates to the treatment of sinus bradycardia, which is extremely common in the first hour or two of infarction and may be observed in the majority of patients with acute inferior infarction if they are seen within the first few hours. Although Goldstein and his associates found that atropine may increase the prevalence of fatal ventricular arrhythmias in experimental infarction (3), this does not usually seem to be the case in humans with acute myocardial infarction and sinus bradycardia. In human infarction, when the heart rate is below 50 per minute and there is evidence of inadequate circulation, intravenous atropine is usually beneficial (5), probably in dosage of at least 0.5–1.0 mg to obviate the possibility of a muscarinic effect of low doses (2).

The indications for electrical DC cardioversion in patients with atrial fibrillation have been further defined. It now appears that this treatment is not indicated in the majority of patients with chronic atrial fibrillation because of the high rate of relapse.

Work is proceeding in the evaluation of new antiarrhythmic agents, such as Norpace

(4), and of oxyprenalol, tolamolol (4) and other beta adrenergic blocking agents. As yet, none of these is approved for general use. Practolol, a promising agent, has been withdrawn because of its tendency to cause cataracts. An effective agent which may be given orally for the long-term treatment of ventricular premature beats and which is free of the toxic effects of quinidine and procainamide is badly needed.

In the management of complete heart block, certain issues seem clarified; others remain uncertain. The value of, and indications for, temporary ventricular electronic pacing in patients with acute cardiac infarction who develop complete AV block are still unclear. The majority of patients with inferior infarction and complete AV block and a supraventricular pacemaker do not appear to require cardiac pacing, although it is usually employed. Patients who develop complete AV block as a complication of anterior infarction require AV pacing as a rule. However, because of their high mortality rate and extensive cardiac damage, it is difficult to show an improvement in survival rate. Cardiac pacing is indicated in most patients who have symptoms related to a persistently slow ventricular rate. In some centers, failure of the sinus pacemaker or "sick sinus syndrome" has emerged as a more common cause of syncope related to bradycardia than is AV block. Patients who have complete AV block with an idioventricular pacemaker should have electronic pacing because of their poor prognosis even though asymptomatic. At this time, asymptomatic patients who have chronic heart disease with evidence of bifascicular block such as right bundle branch block and left anterior hemiblock are not candidates for cardiac pacing since only a small percentage have been shown to progress to complete AV block. This is different from the situation that exists when this conduction disturbance appears in the course of acute infarction, where temporary pacing is probably indicated.

N. O. F.

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Preface

The second edition of CARDIAC ARRHYTHMIAS continues, like the first, to present concise descriptions of current diagnostic methods and current therapies applicable to cardiac arrhythmias commonly encountered in clinical practice. Since proper treatment depends upon correct identification of the arrhythmia, a detailed discussion of the diagnosis, including illustrations, particularly electrocardiograms, where appropriate, precedes the description of treatment. Where more than one treatment regimen is in common use, they are presented in the order of best performance. At the end of each chapter appears a carefully selected list of references to the current literature.

This second edition retains the basic structure of the first, with the addition of a new chapter by Dr. David McCall discussing the pharmacology of antiarrhythmic drugs. Considerable new information concerning the surgical treatment of Wolff-Parkinson-White syndrome is included in Dr. Chou's Chapter 5. Drs. Kastor and Josephson have written a new chapter on the difficult therapeutic decisions in the treatment of atrioventricular block with emphasis on the value of His bundle recordings in reaching a decision in some patients. Drs. Winkle and Harrison have updated the chapter on the use of beta adrenergic blocking agents in the treatment and prevention of cardiac arrhythmias; in addition to the previous information concerning propranolol, they have added much information concerning more recently developed beta blocking drugs. Dr. Donald Romhilt, in a new chapter on the treatment of premature cardiac contractions, emphasizes the difficulty in many instances in deciding on long-term treatment, especially in the absence of heart disease.

Considerable information made available since the first edition about the apparently increasing problems of the sick sinus syndrome is detailed in Chapter 3. Atrial and AV junctional tachycardias are described in a chapter by Dr. Chou; the management of atrial fibrilation and atrial flutter are described in separate chapters. There is now additional information about the long-term results of DC electrical shock in the management of supraventricular arrhythmias. The treatment of ventricular tachycardia is described and brought up-to-date in a separate chapter. Dr. Chou also presents much new information about digitalis-induced arrhythmias, especially with regard to improved diagnostic methods, correlation with serum digoxin levels, and about improved methods of treatment with drugs and cardiac pacing.

Dr. Conway has updated his excellent chapter on the prevention and treatment of cardiac arrhythmias complicating acute myocardial infarction and has emphasized the difficulty in decisions concerning the management of chronic arrhythmias following myocardial infarction. Drs. Dreifus and Satinsky present valuable information concerning the limitations of DC shock in the management of arrhythmias now that we have more experience with that therapeutic tool. Dr. John Holmes has updated his extremely important chapter on cardiac resuscitation.

This book should be of value to physicians specializing in internal medicine and to physicians who engage in family practice or in the general practice of medicine. It will be of interest also to nurses, especially those who work in coronary care and intensive care units, and to paramedical personnel who work in cardiac resuscitation units and emergency care units and life squads. Medical students and residents in training in internal medicine in hospitals will also find this information useful.

N. O. F.

Contents

1 Modern Treatment of Cardiac Arrhythmias: A Perspective

NOBLE O. FOWLER

The first action that should be taken upon detection of a disorder of the heartbeat is to determine the setting in which the arrhythmia occurs. As is rapidly apparent when life is threatened by ventricular fibrillation or extremely rapid paroxysmal tachycardia, one may have to proceed with resuscitative measures, electric shock, or intravenous drugs without a detailed inquiry into the background of the disorder. Yet even in such an emergency, one would avoid electric shock if ventricular tachycardia were caused by digitalis intoxication.

ETIOLOGY OF ARRHYTHMIAS

Table 1–1 indicates some of the etiologic backgrounds of disorders of the heartbeat. Patients with apparently normal hearts may suffer from a variety of disturbances of the cardiac mechanism. Premature cardiac contractions are often unrelated to organic heart disease. They may be precipitated by fatigue, anxiety, overwork, caffeine-containing beverages, tobacco, alcohol, respiratory infections, or sympathomimetic drugs. In such patients treatment consists of a change in the pattern of living and perhaps in sedation. Brief paroxysms of atrial fibrillation may occur in persons with normal hearts, and perhaps 5–10% of patients with paroxysmal ventricular tachycardia have no clinical evidence of organic heart disease.

The myocardial diseases, including myocarditis, may be responsible for premature beats, paroxysmal tachyarrhythmias, and atrioventricular block of all degrees. Acute myocardial infarction is associated with some disorder of the heart beat in over 90% of instances. In infarction prophylaxis must be considered as well as treatment. Cardiac monitoring is needed for the first week or so to detect the patterns of ventricular premature beats, which are warning signs of ventricular tachycardia or fibrillation. Monitoring would also detect the actual occurrence of these disorders and other disturbances of the cardiac mechanism. Paroxysmal tachyarrhythmia in a young person may be a clue to such congenital diseases as the Wolff–Parkinson–White (W–P–W) syndrome or Ebstein's anomaly, or corrected transposition of the great vessels.

Atrial fibrillation and less often atrial flutter, complicate the course of severe mitral valve disease in a large percentage of instances. In such patients correction of the arrhythmia may be difficult unless the valvular deformity is al-

Table 1–1. ETIOLOGY OF CARDIAC ARRHYTHMIAS

Disorder	
Normal heart	Fatigue, caffeine, tobacco, alcohol, sympathomimetic drugs, respiratory infection
Myocardiopathy and myocarditis	Extrasystoles, AV block, atrial fibrillation, paroxysmal tachycardias
Coronary artery disease	Acute infarction
Congenital heart disease	Ebstein's anomaly, atrial septal defect, Wolff–Parkinson–White syndrome, short PR interval with normal QRS, corrected transposition of the great arteries
Rheumatic mitral disease	Atrial fibrillation and flutter
Digitalis intoxication	Extrasystoles, junctional rhythm, AV block; PAT with AV block; ventricular tachycardia
Electrolyte imbalance	Especially hypokaliemia, hyperkaliemia
Disturbances of ventilation and acid-base balance, especially hypoxia and hypocapnea with respiratory alkalosis	Atrial and ventricular tachyarrhythmias
Mitral click-murmur syndrome	Ventricular and atrial tachyarrhythmias
Congenital QT interval prolongation, deafness	Ventricular tachyarrhythmias

leviated surgically. Thyrotoxicosis may precipitate atrial flutter or fibrillation. The arrhythmia may be difficult or impossible to control or revert without treating the hyperthyroidism. A variety of paroxysmal arrhythmias including ventricular tachycardia or fibrillation may be caused by pheochromocytoma. When nodal (junctional) rhythms, ventricular tachycardia, or premature ventricular beats are caused by digitalis intoxication, the withdrawal of digitalis is essential to successful management. When digitalis intoxication has evoked a tachyarrhythmia the administration of potassium may be useful. The use of electric countershock should probably be avoided, since it may provoke ventricular fibrillation in this setting. Other drugs, such as quinidine, may be responsible for premature ventricular contractions or even for syncope or death caused by ventricular fibrillation (2). Electrolyte imbalance, especially potassium deficiency, may cause premature cardiac contractions or junctional rhythms. Hyperkaliemia may be responsible for atrial arrest, cardiac slowing, and syncope. Infusions of glucose and insulin, calcium salts, or sodium bicarbonate are useful in the emergency management of the latter. Especially in patients admitted to intensive care units and undergoing assisted respiration, disturbances of ventilation or acid-base balance may precipitate atrial and ventricular tachyarrhythmias. Hypoxia or respiratory alkalosis may be responsible for this condition (1).

REVERTING THE ARRHYTHMIA

In addition to determining the existence and background of cardiac or other disease which may be responsible for an arrhythmia, the physician must also

determine whether the arrhythmia should be reverted to a sinus mechanism, and whether there are unjustifiable risks in permitting the arrhythmia to continue without treatment. Premature cardiac contractions may be harmless and may produce no symptoms; on the other hand, even though benign, they may cause disturbing palpitation. At the other extreme, when premature beats are frequent or multifocal they may warn of impending paroxysmal ventricular tachycardia or ventricular or atrial fibrillation. Atrial fibrillation or flutter, especially when associated with a rapid ventricular rate, may significantly impair cardiac function leading to heart failure and pulmonary edema. The latter is especially dangerous in mitral stenosis.

Atrial fibrillation increases the danger of systemic or pulmonary embolism and may result in disturbing palpitation. Yet in some patients, permanent reversion to a sinus mechanism is difficult or impossible and the only practical therapy is to slow the ventricular rate with digitalis, and perhaps to use supplemental anticoagulant therapy. Ventricular tachycardia may lead to shock or pulmonary edema, or to death from cardiac arrest. It is a special risk because of its frequent association with severe organic heart disease, the loss of atrial kick to ventricular filling, and the abnormal site of initial ventricular activation. Complete atrioventricular block is attended by the risk of syncope or sudden death caused by cardiac slowing, standstill or ventricular fibrillation, in addition to heart failure or renal failure.

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2 Pharmacology of Antiarrhythmic Drugs

DAVID MCCALL

The general principles to be followed in the management of cardiac arrhythmias are well defined in a recent publication by Winkle and his colleagues (68). These principles include an exact characterization of arrhythmias and the definition and treatment of underlying heart disease, if present. If the arrhythmias are suitable for pharmacologic suppression, precise therapeutic goals should be set documenting the efficacy of the drugs. Although in their article (68) these principles are directed mainly towards the therapy of ventricular arrhythmias, they are equally applicable to atrial arrhythmias.

Selection of the appropriate antiarrhythmic agent is based upon a knowledge of the possible underlying arrhythmogenic mechanisms combined with a knowledge of the electrophysiologic actions and pharmacokinetics of the available drugs. It is necessary to consider the electrophysiologic properties of an antiarrhythmic drug combined with a knowledge of its rates and modes of excretion, metabolic pathways and an understanding of the degree of plasma protein binding of that agent. The decision to pharmacologically suppress cardiac arrhythmias may be a decision involving a very short time span, such as suppression of arrhythmias associated with an acute myocardial infarction or myocarditis. However, it may be a decision subjecting the patient to pharmacologic intervention for the remainder of his life. In the latter setting it becomes extremely important to select an agent which will achieve satisfactory suppression of the arrhythmia combined with a minimal incidence of adverse side effects.

In any situation the presence of a cardiac arrhythmia is a reflection of altered underlying cellular electrophysiology. All of the antiarrhythmic drugs have effects on both normal and abnormal cardiac electrophysiology. A review of these topics is necessary to provide a better understanding of the mechanisms of the action of antiarrhythmic drugs. During the past decade considerable evidence has accumulated as to the basic electrophysiologic changes underlying many cardiac arrhythmias. These electrophysiologic changes have been the subject of more extensive and detailed reviews (18, 33, 39, 62, 64), and only a brief revision is within the scope of this chapter.

The first of these mechanisms to be considered is that of enhanced automaticity. This term is used to describe an increased rate of spontaneous discharge from subsidiary or ectopic pacemaker tissue situated either in the atrium, junctional tissue, Purkinje system or ventricular myocardium. Electrophysiologic studies have indicated that the most important determinant pacemaker activity is the slope of the slow intrinsic diastolic depolarization phase of

pacemaker tissue. Enhanced automaticity is associated with an increase in the diastolic depolarization rate during this phase, which in turn may be associated with various underlying conditions. Increased rate of spontaneous diastolic depolarization has been observed in ischemic or hypoxic myocardium, in ventricular dilatation, such as occurs in heart failure, in hypokalemia, and exposure to endogenous or exogenous catecholamine activity. Enhanced automaticity is the probable mechanism underlying atrial, junctional and ventricular parasystolic rhythms. Arrhythmias based on enhanced automaticity are therefore by definition considered tachyarrhythmias. On the other hand suppression of automaticity will result in a bradyarrhythmia. Sinus bradycardia, for example, is due to decreased automaticity within the sinoatrial node mediated via acetyl choline released by vagal stimulation, ischemia of the pacemaker tissue or depletion of endogenous catecholamines. Altered automaticity may lead to both tachy and bradyarrhythmias, the more significant, however, being the tachyarrhythmias due to enhanced diastolic depolarization of latent pacemaker tissue.

The second important mechanism to be considered is that of decreased conductivity of the electric impulse within the cardiac tissue, resulting in impaired impulse transmission and decremental conduction. Decreased conduction velocity of the electric impulse and decremental conduction are capable of producing either unidirectional or bidirectional block, the former being largely responsible for the development of reentrant arrhythmias. Reentrant activity is used to describe a situation of continuous impulse propagation at a conduction rate slow enough to permit recovery from the refractoriness of the initiating focus before the circuit is complete. In this situation the slowly propagated impulse returns to the initiating point at a time when its effective refractory period is over and therefore is susceptible to restimulation, thereby reinitiating the circuit. Unidirectional block or decremental conduction through a localized area of myocardium is a necessary prerequisite for reentry since the initial response must fail to excite some area of tissue which is thereby capable of supporting a reentrant response.

Although reentrant arrhythmias may arise in any part of the myocardium, certain regions appear to be more vulnerable than others. In the atrium the distribution of specialized conduction networks provides the appropriate pathways for the development of the suspected circuit reentrant arrhythmia, presenting as atrial flutter. More recently reentrant pathways within the atrioventricular node have been associated with the occurrence of paroxysmal atrial tachycardia. The tachyarrhythmia appears to be sustained by reentry within the atrioventricular node itself. The peripheral ventricular conducting system, including Purkinje fibers and myocardial tissue, is probably more commonly implicated, resulting in reentrant ventricular premature beats. These premature beats will occur most often as coupled beats, usually with a fixed coupling interval. Sustained reentry in this setting may very easily result in ventricular tachycardia. Total suppression of conductivity, indicating bidirectional block, if strategically located within the conducting system, will produce the rhythms of heart block. This may be partial or complete or may reflect a block within

one of the more peripheral areas of the conducting system, such as occurs in left or right bundle branch block, or in one of the individual fascicles comprising the left bundle system.

A third major electrophysiologic mechanism of arrhythmogenesis is that of temporal dispersion of action potential duration. This refers to a disparity in the duration of the individual action potentials of neighboring myocardial fibers following simultaneous activation. This process may be associated with focal reexcitation, but is basically different from reentrant activity since it does not require a complete circular pathway, nor does it require unidirectional block. The situation in this instance is that of the presence of fibers which have already repolarized, and hence are beyond their effective refractory period. These repolarized fibers are in close proximity to fibers which remain depolarized for much longer. This sets up a local potential difference between adjacent fibers, which may be sufficient to exceed the threshold for restimulation of the repolarized fibers. These fibers are then restimulated and a focal reexcitation process initiated. This asynchronous recovery of the membrane potential is generally associated clinically with closely coupled premature beats, although some controversy still exists as to the prominence of this reexcitation mechanism. Several factors are known to contribute to nonuniformity of action potential duration. These include digitalis toxicity, localized ischemia, hypokalemia and excess of various antiarrhythmic agents.

Although theoretically it is simple to conceptualize of these three basic mechanisms producing different types of cardiac arrhythmias, in practice any combination of these mechanisms may well be operative. Pharmacologic therapy therefore has to be directed towards the correction of the underlying electrophysiologic mechanism thought most likely in any given situation.

Antiarrhythmic agents produce profound electrophysiologic changes in cardiac tissue. On the basis of their electrophysiologic effects, antiarrhythmics have been classified into two major groups by Bassett and Hoffman (5). The more important of these electrophysiologic actions are summarized in Table 2–1. The drugs of group 1, including quinidine, procainamide, and propranolol, produce somewhat different electrophysiologic effects from those drugs of group 2, including lidocaine and diphenylhydantoin. All drugs listed

Table 2–1. ELECTROPHYSIOLOGIC ACTIONS OF ANTIARRHYTHMIC DRUGS

Electrophysiologic properties	Group I			Group II
	Quinidine	Procainamide	Propanolol	Lidocaine Diphenyl hydantoin
Automaticity	↓		↓	↓
Excitability	↓		↓	—
Membrane responsiveness	↓		↓	— or ↑
Effective refractory period (ERP)	↑		↓	↓
Action potential duration (APD)	↑		↓	↓
ERP relative to APD	↑		↑	↑

↑ Increased ↓ Decreased — Unchanged

in Table 2–1 decrease automaticity by slowing the rate of diastolic depolarization in subsidiary pacemaker tissue. Quinidine and procainamide increase both action potential duration and effective refractory period, while diphenylhydantoin and lidocaine produce a decrease in both of those parameters. Propranolol, although included with group 1 drugs, differs from the other two drugs in this group in that it causes a decrease in action potential duration and effective refractory period similar to that seen with drugs of group 2. It is of interest that all of the drugs possess the property of increasing effective refractory period duration relative to total action potential duration. Since this effect is common to all antiarrhythmic agents listed and since all are effective in most clinical situations, it may be that this particular property represents the most important electrophysiologic requirement of an antiarrhythmic drug. At the present time it is impossible to select any one of the electrophysiologic characteristics which, in any given situation, will be arrhythmia suppressing. A combined consideration of the electrophysiologic basis of arrhythmias and a knowledge of the electrophysiologic actions of the antiarrhythmic drugs must act as a guide in the selection of an appropriate suppressive agent.

In addition to an understanding of the electrophysiologic effects of the antiarrhythmic drugs, the selection, dosage, and frequency of administration of any particular drug must be based on an understanding of the pharmacokinetic properties of that agent. Although the properties of the individual agents will be discussed with respect to the individual drugs, an outline of the general principles of antiarrhythmic drug administration should be considered at this point. For more extensive treatment of this subject the review of articles by Winkle and his colleagues (68) and Moss and Patton (51) are recommended to the reader.

Since both the therapeutic efficacy and the incidence of adverse side effects of most of the commonly used antiarrhythmic agents show a relationship to plasma drug level, it is important that plasma drug levels be monitored regularly. Knowledge of the kinetic characteristics of the individual drug must be employed in choosing the appropriate dose and frequency of administration. Pharmacologic principles dictate that antiarrhythmic drugs be given on a rigid time schedule, which in most cases, will include the necessity of the patient taking the drug at some time during the night. It is the experience (68) that most patients taking antiarrhythmic drugs do not take them on a regular dose schedule and therefore do not have the benefit of continuously therapeutic blood levels. Administration of an antiarrhythmic agent to a patient, whether by repeated regular oral dosage or by continuous intravenous infusion, requires a basic understanding of the rate of excretion of the drug, the amount of plasma protein binding expected, and the rate of metabolism, together with the various metabolic pathways involved. It is also important to consider the compartment or compartments throughout which the drug is distributed and the manner in which it is distributed, since this will affect the ultimate concentration of the agent at its desired therapeutic target organ. To consider all of these parameters in a scientifically accurate way would necessitate the use of complex mathematic formulas, which

in most cases is beyond the scope of practical clinical care of the patient.

A somewhat more simplified approach, could be summarized as the "plateau principle" (31). This concept, summarizing the kinetics of drug accumulation in the body, incorporates pharmacodynamics of distribution, binding, degradation, and excretion. It is fundamental to the understanding of steady state, constant rate infusions and to the dosing interval of intermittently administered agents. The concept does incorporate some assumptions as to the kinetics of absorption and elimination, but in the light of present knowledge these assumptions can be reasonably incorporated into our clinical therapeutic regimes. The concept defines that the establishment of a stable serum level of the drug is determined primarily by the rate of excretion, or elimination, from the body, which also determines the so-called biologic halftime of the agent. During a constant rate of drug infusion it was found (31) that plasma levels increased steadily and reached 90% of the desired plateau blood level after approximately three half-times had elapsed. The implications of this are clear, for example, in the case of lidocaine. Lidocaine has a half-time of about 100 minutes (61), and would require about 5–6 hours of constant infusion before a steady therapeutic blood level is reached. When contemplating continuous infusions it is apparent that a steady plasma level cannot be rapidly obtained, except by the administration of large initial loading doses given at the time of initiation of the continuous infusion. This is now the usually recommended procedure. In addition (31) if one shifts from one steady state of infusion to another in an attempt to increase the plasma drug level, it will again take approximately three half-times to reach 90% of the anticipated new plateau steady state. For this reason it is also recommended that when the infusion rate is increased in an attempt to elevate the plasma level of an agent, a further bolus injection be given at the time of the increase.

The principles outlined above for continuous infusion of antiarrhythmic agents can also be used to determine the appropriate dosing interval of intermittently administered oral drugs. Since the overall principle in the administration of antiarrhythmic therapy is to achieve constant serum levels as nearly as possible, one should accept fluctuations of effective drug concentrations of no greater than 50% in any given 24 hour interval. Since a decrease of 50% in the serum level requires a time interval equal to the half-time of excretion or biologic half-time of the drug, it follows that the dosing interval of any agent should approximately equal the known biologic half-time of that agent. The actual concentration of an agent in the blood, is a reflection not only of the rate of excretion and dosing interval, but also of the amount given together with other variables indicated above, such as plasma protein binding and variable compartmental distribution. It is therefore imperative that blood levels of the drug should be obtained during the initial phases of stabilization on an agent so that a guide as to the frequency and amount of drug administration to any given patient can be obtained. The rate of excretion of a drug or its rate of metabolic conversion may be significantly altered by various disease states. For this reason it is not possible to set down hard and fast rules as to the amount and frequency of administration of any given drug and in the following