RATIONALE OF DRUG THERAPY

By Edward K. Chung

INTRODUCTION

Various anti-arrhythmic agents are essential in preventing and treating cardiac arrhythmias in order to prevent the untoward sequelae which frequently follow. These untoward sequeal may include: the development of congestive heart failure, worsening of pre-existing congestive heart failure or myocardial infarction, Adams-Stokes-syndrome, hypotension, shock, renal or cerebral insufficiency, aggravation of anginal pain, development of thromboembolic phenomena, various symptoms from the arrhythmia itself, such as palpitations, skipped heart beats, etc. and even sudden death.

Since DC cardiverters and artificial pacemakers have become readily available, the therapeutic results in the management of arrhythmias have improved markedly in the past decade. Thus, the use of large amounts of anti-arrhythmic drugs can often be avoided, especially in light of current knowledge. Nonetheless, various pharmacological agents are still indispensable in the prevention, as well as the treatment of various arrhythmias, in conjuction with the use of DC cardioverters and artificial pacemakers.

The best therapeutic results can be obtained when the precise diagnosis of the arrhythmia is known, because certain drugs are more effective or even almost specific for particular arrhythmias. For instance, digitalis is usually the drug of choice in the treatment of various supraventricular tachyarrhythmias, especially atrial fibrillation with rapid ventricular response. Conversely, digitalis is ineffective or even contraindicated in the treatment of ventricular tachyarrhythmias.

In addition to the correct diagnosis of the arrhythmia, the underlying etiological factors also significantly influence the therapeutic result. For example, ventricular tachycardia associated with acute myocardial infarction is best treated with lidocaine, whereas digitalis-induced ventricular tachycardia responds best to diphenylhydantoin or potassium.

Prevention of the recurrence of tachyarrhythmias is another important aspect of management. For this reason, maintenance therapy with digitalis and many other anti-arrhythmic drugs is often necessary for long periods of time or even indefinitely. Quinidine is known to be the best agent to prevent recurrence of atrial fibrillation or flutter, whereas procainamide is known to be the best agent for the prevention of ventricular tachyarrhythmias for long-term therapy. Propranolol has been shown to be the most effective agent in the treatment of arrhythmias precipitated by exercise, emotional stress, or excessive sympathetic stimulation, and in arrhythmias related to the Wolff-Parkinson-White syndrome. Bretylium tosylate is still an investigative agent which has been reported to be very effective in the treatment of refractory ventricular tachyarrhythmias.

Anti-bradyarrhythmic agents are much less frequently used at present, because of the ready availability of artificial pacemakers. Commonly used anti-bradyarrhythmic agents include atropine and isoproterenol, especially during acute myocardial infarction.

Anti-Tachyarrhythmic Agents

As emphasized previously, the best therapeutic results can be obtained when the precise diagnosis of the arrhythmia is known since some drugs are more effective or even almost specific for certain arrhythmias. In addition, indications of various antitachyarrhythmic agents vary markedly depending upon the underlying cause for the tachycardia. The most commonly used tachyarrhythmic agents include cardiac glycosides, quinidine, lidocaine (Xylocaine), procaine amide (Pronestyl), diphenylhydantoin (Dilantin) and propranolol (Inderal).

Division of Cardiology, Department of Medicine West Virginia University, School of Medicine, Morgantown, W. Va.
Professor of Medicine, Director, Electrocardiographic Laboratory.

Cardiac Glycoside[1-3]

Cardiac glycoside has probably been the most valuable drug available in our medical practice since the time digitalis was introduced by a British physician, William Withering in 1785.[1] It is well documented that cardiac glycoside is an essential drug in the management of congestive heart failure regardless of the underlying heart disease. It is also essential in various supraventricular tachyarrhythmias, particularly atrial fibrillation with rapid ventricular response.

Cardiac glycoside has various actions on various organs including the heart, kidney, and peripheral vessels. The most important effects of digitalis, however, are the inotropic action and the electrophysiologic effects on the heart. Cardiac glycoside primarily increases the strength and efficiency of myocardial contractility. This action is particularly remarkable when congestive heart failure is present. The electrophysiologic effects, both direct and indirect (vagal stimulating action), are very important when one considers the therapeutic effects upon various supraventricular tachyarrhythmias, and the development of various digitalis-induced cardiac arrhythmias. These electrophysiologic effects are considerably different in various parts of the heart, and these effects differ according to the amounts of glycoside given (Table I).

The choice of the proper digitalis preparation and method of administration directly influences the therapeutic effect of digitalis and the incidence of digitalis intoxication. By and large, there are 4 ways to digitalize in most clinical situations: Namely, very rapid parenteral digitalization (within 12 hours), rapid oral digitalization (within 24-48 hours), moderately rapid oral digitalization (within 2-3 days) and slow oral digitalization (within 5-8 days). The choice depends upon the degree of urgency, the nature of the underlying heart disease and/or the presence or absence of cardiac arrhythmias. For urgent situations such as acute pulmonary edema due to left ventricular failure, or supraventricular tachyarrhythmias, very rapid parenteral digitalization is indicated. Short-acting preparations such as digoxin, deslanoside or ouabain are commonly used. Rapid oral digitalization (within 24 hours) may be used when patients are suffering from acute congestive heart failure and/or supraventricular tachyarrhythmias; but where the clinical situation is not urgent enough to require very rapid parenteral digitalization. In these situations, therapeutic effect is reached within 24 to 48 hours. Moderately rapid oral digitalization (within 2-3 days) is preferred when the patient shows well developed, but not acute congestive heart failure. It is not usually recommended when congestive heart failure is associated with, or due to, supraventricular tachyarrhythmias. This method can be used either in the hospital or in the outpatient clinic. Slow oral digitalization (within 5-8 days) is very useful in patients with mild congestive heart failure without any acute symptoms or supraventricular tachyarrhythmias. This method is frequently used for ambulant patients in clinic or in private offices. This method, of course, can be used in the hospital as well. A detailed description regarding methods of digitalization is shown in Table II. In spite of the fact that there is marked variation in dosage in different individuals, and even variations in the same individual, extensive clinical experience enables us to set guidelines concerning average doses, usual range of dosages for full digitalization, and maintenance use (Table III). Precise information regarding the time of action and dissipation of various digitalis preparation is indispensable in order to obtain the best therapeutic effect and to avoid digitalis toxicity. It is extremely important to remember that the additional dose should not be given before the maximum effect of the first dose of glycoside is reached. Otherwise, digitalis toxicity may often be unavoidable. When there are various modifying factors, the time of action and dissipation of digitalis preparations may be significantly altered. This is particularly true when marked renal failure is associated with heart failure. Detailed des-

TABLE I

ELECTROPHYSIOLOGICAL EFFECTS OF DIGITALIS ON THE HEART

	Dosage	Automaticity*	Excitability**	Conductivity***
Sinus Node	Therapeutic	↓	—	—
	Toxic	↓ ↓	—	—
S-A Junction	Therapeutic	—	—	↓
	Toxic	—	—	↓ ↓
Atria	Therapeutic	↓	↓	↓
	Toxic	↑	↑	↑
A-V Node	Therapeutic	↓	↓	↓
	Toxic	↑ ↑	↑	↓ ↓
Purkinje fibers	Therapeutic	↓	↓	↓
	Toxic	↑	↑	↓ ↓
Ventricles	Therapeutic	↓	↓	↑
	Toxic	↑ ↑	↑	↓

*Automaticity: is defined as the ability to initiate an impulse spontaneously without the benefit of an external stimulus.

**Excitability: is the ability to respond to a stimulus.

***Conductivity: is the ability to conduct an impulse from one area to other area of the heart.

↑ : Increased
↑ ↑ : Markedly increased
↓ : Decreased
↓ ↓ : Markedly decreased

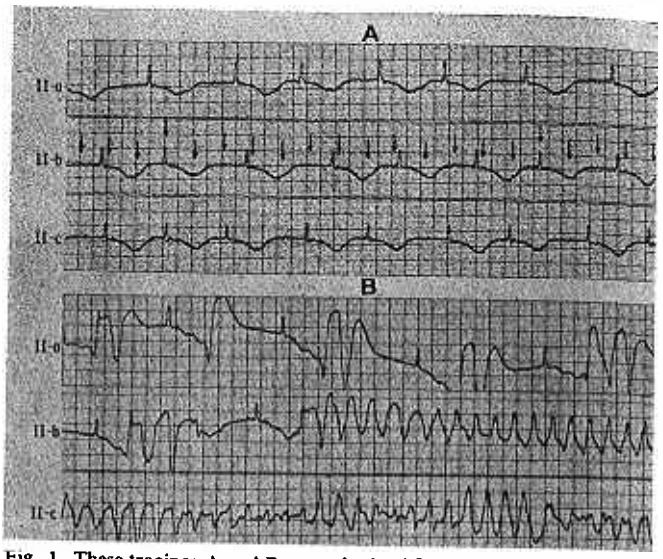

Fig. 1. These tracings A and B were obtained from a 56-year-old woman with history of anterior myocardial infarction 6 months previously. Leads II-a, b and c are continuous in both tracings A and B. In tracing A, arrows indicate P waves. The rhythm is atrial tachycardia (atrial rate: 150/min.) with varying degree A-V block. This rhythm disturbance is thought to be due to digitalis toxicity. Note a marked prolongation of the Q-T interval (0·60 second) due to quinidine effect. Tracing B taken several hours later shows ventricular fibrillation triggered by ventricular premature contractions which are superimposed during the vulnerable period ("R-on-T phenomenon"). The R-on-T phenomenon in this tracing is due to prolonged Q-T interval resulting from quinidine effect. The atrial mechanism is the same as that of tracing A (atrial tachycardia with varying A-V block).

TABLE II

METHODS OF DIGITALIZATION

	Very rapid digitalization (within 12 hrs.)	Rapid digitalization (within 24 hrs.)	Moderately rapid digitalization (within 2-3 days)	Slow digitalization (within 5-8 days)
Digoxin	0·5-1 mg. I-V injection initially, then 0·25-0·5 mg. q 2-4 hrs. as needed	1-1·5 mg. by mouth initially, then 0·5 mg. q 6 hrs. until digitalized	0·5 mg. t.i.d. by mouth for 2-3 days until digitalized	0·25 mg. t.i.d. by mouth for 5-8 days until digitalized
Deslanoside	0·8-1·6 mg. I-V injection initially, then 0·4 mg. q 2-4 hrs. as needed	—	—	—
Ouabain	0·25-0·5 mg. I-V injection initially, then 0·1 mg. q ½ hr. as needed	—	—	—
Digitoxin	—	0·8 mg. by mouth initially, then 0·2 mg. q 6 hrs. until digitalized	0·2 mg. t.i.d. by mouth for 2-3 days until digitalized	0·1 mg. t.i.d. by mouth for 5-8 days until digitalized
Digitalis leaf	—	0·8 g. by mouth initially, then 0·2 g. q 6 hrs. until digitalized	0·2 g. t.i.d. by mouth for 2-3 days until digitalized	0·1 g. t.i.d. by mouth for 5-8 days until digitalized

TABLE III

FULL DIGITALIZATION AND MAINTENANCE DOSES

	Digitalizing doses within 24-48 hrs.				Maintenance doses	
	I-V or I-M administration		Oral administration			
	Average	Usual range	Average	Usual range	Average	Usual range
DIGOXIN	1·5 mg.	1 -2·5 mg.	2·5 mg.	1·5-4 mg.	0·25 mg.	0·125-0·75 mg.
DESLANOSIDE	1·6 mg.	1·2-2 mg.	—	—	—	—
OUABAIN	1 mg.	0·5-1·2 mg.	—	—	—	—
DIGITOXIN	1·2 mg.	1 -2 mg.	1·5 mg.	1·2-2 mg.	0·1 mg.	0·05 -0·2 mg.
DIGITALIS LEAF	—	—	1·5 g.	1·2-2 g.	0·1 g.	0·05 -0·2 g.

criptions of the time of action and dissipation of various digitalis preparations are shown in Table IV. In general, serum digoxin levels of 2·0 ng./ml. or below, and digitoxin levels of 20 ng./ml. or below (by radioimmunoassay method) are considered to be nontoxic. Digoxin levels below 0·4 ng./ml. or digitoxin levels below 10 ng./ml. usually indicates underdigitalization.

When the patient develops digitalis toxicity, the drug is no longer beneficial to that patient. As shown in Table V, the various manifestations can be arbitrarily divided into 2 major groups, namely, common and uncommon findings. In addition, the various symptoms of digitalis intoxication may be divided into 4 major categories including gastrointestinal disturbances, cardiac manifestation, visual disturbances and neurological disturbances. Non-specific signs or symptoms such as allergic reactions, idiosyncracy, thrombocytopenia and gynecomastia are *not* true manifestations of digitalis intoxication.

Among various manifestations of digitalis toxicity, the most important and the most common finding is various digitalis-induced arrhythmias (Fig. 1). In particular, frequent multifocal ventricular premature contractions and non-paroxysmal A-V nodal (junctional) tachycardia, especially in the presence of atrial fibrillation, are the commonest arrhythmias in digitalis intoxication. Another important sign of digitalis toxicity is the worsening of pre-existing congestive heart failure.

The most important treatment of digitalis toxicity is the immediate discontinuation of the drug rather than reducing the dosage. Most patients with mild digitalis toxicity, such as first degree A-V block, sinus bradycardia and occasional ventricular premature contractions, can recover from digitalis toxicity by discontinuing the drug for several days. If digitalis toxicity is manifested by serious cardiac arrhythmias, more active therapeutic measures are required, although there are no drugs that have a proven antagonism to the action of digitalis. Among many agents, diphenylhydantoin (Dilantin) and potassium have proved to be the most effective in terminating various digitalis-induced tachyarrhythmias.

Quinidine[4-8]

Quinidine has probably been the most valuable antiarrhythmic agent available in the past 50 years. Quinidine has 2 major effects, namely, direct and indirect. The direct effect of the drug is on the cell membrane, while the indirect effect is anticholinergic in nature. As a result of the net clinical effects of the combined anticholinergic and direct actions, a marked prolongation of the refractory period in the atria and to a lesser degree in the ventricles is produced. In addition, a shortening of the refractory period in the A-V junction is induced by quinidine. The sinus rate tends to be slowed by the direct effect of quinidine but the indirect (vagolytic) effect tends to reverse this. As a result, the sinus rate may not be altered significantly by quinidine or it may even be accelerated.

Following oral administration of quinidine, gastrointestinal absorption begins within 15 minutes. Approximately 80% of quinidine is bound to albumin in the plasma and within 2-4 hours, the peak concentration is reached. As far as the excretion of the drug is concerned, 40% disappears from the blood in 6 hours, 75% in 12 hours and 90% in 24 hours following a single oral dose. The maximum serum concentration is observed in 48-96 hours when quinidine is administered every 4 hours. Practically all of the administered quinidine is excreted in the urine with 10-50% unchanged and the remainder as hydroxylated derivatives.

Quinidine has been an indispensable drug to convert atrial fibrillation or flutter to sinus rhythm. Before DC cardioverters were available, large amounts of quinidine sulfate had to be used to restore sinus rhythm, but it is no longer necessary to do so except when a DC cardioverter is not available. At present, the role of quinidine is primarily to prevent the recurrence of atrial fibrillation or flutter following the restoration of sinus rhythm by either digitalization or DC shock. In addition, quinidine is also useful in the treatment of various acute supraventricular as well as ventricular tachyarrhythmias. In acute tachyarrhythmias, quinidine is found to be more effective for the treatment of supraventricular than ventricular ones. Quinidine is also useful in the suppression of premature beats, especially those of supraventricular origin.

For the treatment of acute tachyarrhythmias, quinidine gluconate 0·8 gm. diluted in 200 cc. of 5% dextrose in water may be given intravenously at a rate of about 25 mg. per minute, under continuous electrocardiographic monitoring. Intramuscular administration of quinidine gluconate may be carried out by giving 0·4 to 0·6 gm. initially, followby 0·4 gm. every 2 to 4 hours as needed. Total dosage by the intramuscular route should not exceed 2 to 2·4 gm. (Table II). The usual maintenance dosage of quinidine sulfate for the prevention of recurrence of various arrhythmias is 0·3 to 0·4 gm. every 6 hours.

The therapeutic effects of quinidine may be observed at blood levels of 2-5 mg./L. although at times, concentrations of 5-8 mg./L. are needed in some patients. When the blood levels exceed 8 mg./L., quinidine toxicity is often observed.

Mild toxic manifestations include nausea, vomiting, diarrhea, tinnitus, slight impairment of hearing and vision, and slight widening of the QRS complex. When quinidine toxicity is advanced, the above manifestations become more severe. Thus, the patient may develop blurring of vision, disturbed color perception, photophobia, diplopia, abdominal pain, headache, confusion, and ventricular tachyarrhythmias. When the patient has an unusual sensitivity or idiosyncracy to quinidine, he may develop respiratory depression, hypotension, convulsions, urticaria, macular or papular rashes, fever, thrombocytopenia, hemolytic anemia and even sudden death. (Table VI). It should be noted that the patient may develop ventricular fibrillation because of the "R-on-T" phenomenon resulting from quinidine-induced Q-T prolongation (Fig. 1).

Procaine Amide (Pronestyl)[9-13]

Procaine amide had been the traditional drug of choice in the treatment of ventricular tachycardia until lidocaine was proven to be a safer and more effective agent. Large amounts of Pronestyl had often been used in the treatment of ventricular tachycardia, especially until DC cardioverters became readily available.

Pronestyl has very similar electrophysiological effects to quinidine. Pronestyl slows electrical conduction, increases the refractory period, and depresses diastolic depolarization and automaticity. Pronestyl has an indirect vagolytic action, and A-V conduction may be facilitated when low doses are used. However, the direct effect of Pronestyl is to produce depression of A-V conduction at higher doses. The therapeutic levels are easily achieved by oral administration since Pronestyl is almost completely absorbed from the gastrointestinal tract.

The maximal plasma level is observed within 60 minutes following oral administration of a single dose. When the drug is administered intravenously, the therapeutic effects are observed at once, and intramuscular injection produces almost as rapid an effect. The maximum effect of Pronestyl is reached within a few to 30 minutes, and the duration of action lasts about 6 hours. Pronestyl should be used with particular caution in patients with renal insufficiency since 60% of the drug is excreted by the kidneys in unchanged form.

Although procaine amide has very similar electrophysiological actions to quinidine, the former drug has been used primarily in the treatment of ventricular tachyarrhythmias. At present, the primary indication for Pronestyl is in the prevention of recurrences of ventricular tachyarrhythmias following their termination by DC shock and/or intravenous lidocaine. Pronestyl is also effective in the treatment of supraventricular tachyarrhythmias, although it is not the primary drug of choice. Pronestyl has been used in place of quinidine when the patient is unable to take the latter drug. At present, large dosages of parenteral Pronestyl are used only when a DC cardioverter is not available and lidocaine is found to be ineffective. Pronestyl is very effective in the suppression of ventricular premature beats.

When intravenous Pronestyl has to be used, 1 to 2 gm. of the drug diluted in 200 cc. of 5% dextrose in water is administered by continuous intravenous drip at a rate of

TABLE IV

TIME OF ACTION AND DISSIPATION OF DIGITALIS PREPARATIONS

Drugs/Route	Onset of action		Maximum effect		Dissipation
	I-V or I-M	Oral	I-V or I-M	Oral	
DIGOXIN	10-30 mins.	1-2 hrs.	2-3 hrs.	3-6 hrs.	3-6 days
DESLANOSIDE	10-30 mins.	—	2-3 hrs.	—	3-6 days
OUABAIN	3-10 mins.	—	½-1 hr.	—	12 hrs.-3 days
DIGITOXIN	—	2-4 hrs.	—	8-10 hrs.	2-3 weeks
DIGITALIS LEAF	—	2-4 hrs.	—	8-10 hrs.	2-3 weeks

TABLE V

MANIFESTATIONS OF DIGITALIS TOXICITY

Symptoms	Common	Uncommon
G-I	Anorexia, nausea, vomiting	Abdominal pain, constipation, diarrhea, hemorrhage
CARDIAC	Worsening of CHF, VPC, PAT c block, non-paroxysmal A-V NT, A-V Block, SB	AF, AFl., VT, VF, Sinus arrest, S-A block, APC, NPC
VISUAL	Color vision (green or yellow) c halos	Blurring or shimmering vision, scotoma, micropsia or macropsia, amblyopia
NEUROLOGICAL	Fatigue, headache, insomnia, malaise, confusion, vertigo, depression	Neuralgia, convulsions, paresthesia, delirium, psychosis
NONSPECIFIC		Allergic reaction, idiosyncracy, thrombocytopenia, gynecomastia

CHF : Congestive heart failure
VPC : Ventricular premature contraction
APC : Atrial premature contraction
NPC : Nodal premature contraction
PAT : Paroxysmal atrial tachycardia
NT : Nodal tachycardia
VT : Ventricular tachycardia
VF : Ventricular fibrillation
AF : Atrial fibrillation
AFl : Atrial Flutter
SB : Sinus bradycardia
G-I : Gastrointestinal

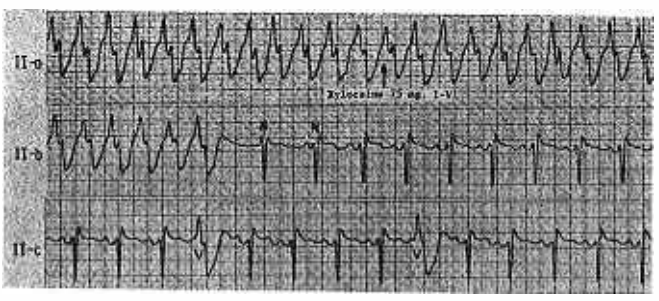

Fig. 2. Leads II-a and b are continuous. Ventricular tachycardia (rate: 155/min.) is terminated by intravenous injection of Xylocaine, 75 mg. (indicated by arrow). The configuration of the QRS complex of the ventricular premature contraction (marked V) and the tachycardia is identical. This finding proves that the tachycardia is ventricular in origin. Note two A-V nodal (junctional) premature beats (marked N) in lead II-b. The tachycardia is associated with acute anterior myocardial infarction. (Reproduced from Edward K. Chung, Principles of Cardiac Arrhythmias Baltimore, Williams & Wilkins Co., 1971).

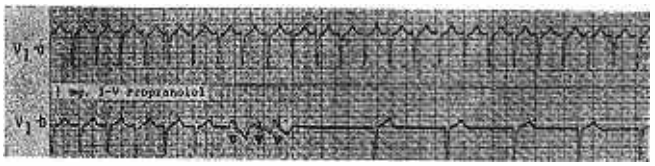

Fig. 3. Leads V1-a and b are not continuous. Supraventricular (most likely atrial) tachycardia (rate: 150-175/min.) is terminated by intravenous injection of propranolol, 1 mg. Note ventricular group beats (marked V) before the restoration of sinus rhythm.

TABLE VI COMMON ANTIARRHYTHMIC DRUGS

Drugs	Full Dosage	Maintenance Dosage	Onset of Action	Maximum Effect	Duration of Action	Indications	Toxicity	
							Dosage-dependent	Dosage-independent
Lidocaine (Xylocaine)	75-100 mg. direct I-V q 10-20 min. as needed (total: 750 mg.) or 200-250 mg. I-M q 10-20 min. as needed	1-5 mg./min. I-V infusion	At once	At once	Minutes	Primary: V. tachyarrythmias Secondary: S.V. tachyarrhythmias	Dizziness, drowsiness, confusion, muscle twitching, disorientation, euphoria, cardiac and respiratory depression, convulsion, hypotension, A-V & I-V block	
Procaine amide (Pronestyl)	1-2 gm./200 cc. 5% D/W I-V drip, 100 mg. q 2-4 min. (1 gm. in ½-1hr.) (total: 2 gm.) or 1 gm. p.o. initially, then 0·5 gm. q 2-3 hrs. (total: 3.5 gm.)	0·25-0·5 gm. q 6 hrs. (P.O.)	At once Rapid	Minutes 1-2 hrs.	6 hrs. 6-8 hrs.	Primary: V. tachyarrhythmias Secondary: S.V. tachyarrhythmias	A-V & I-V block, ventricular arrhythmias, LE, nausea, vomiting, lymphadenopathy, hypotension, convulsion	Allergic manifestations (eosinophilia, urticaria) agranulocytosis
Quinidine Glucorate	0.8 gm./200 cc 5% D/W I-V drip. 25 mg./min. or 0·4-0·6 gm. I-M initially then 0·4 gm. q 2-4 hrs. (total; 2·6 gm.)		10-15 min. 10-15 min.	Not immediate 30-90 min.	6-8 brs. 6-8 hrs.	Primary: S.V. tachyarrhythmias Secondary: V. Tachyarrhythmias	A-V, I-V block, nausea, vomiting, photophobia, diplopia, headache, tinnitus, diarrhea, ventricular arrhythmias	Respiratory depression, hypotension, convulsion, rashes (macular or papular), thrombocytopenic purpura, thrombocytopenia, hemolytic anemia
Quinidine Sulfate	Oral route (see text)	0·3-0·4 gm. q 6 hrs. (P.O.)		2-3 hrs.	6-8 hrs.			
Diphenylhydartoin (Dilantin)	125-250 mg. I-V q 10-20 min. as needed (total: 750 mg./hr.)	100-200 mg. q 6 hrs. (P.O.)	At once	Minutes	4-8 hrs.	Primary: Digitalis-induced arrhythmias Secondary: Nondigitalis-induced arrhythmias (ventricular)	Cardiac depression, hypotension A-V, S-A block, sinus bradycardia, ataxia, tremor, gingival hyperplasia	Allergic manifestations, (urticaria, purpura and eosinophilia)
Propranolol (Inderal)	1-3 mg. I-V initially, then second dose may be repeated after 2 min. Additional medication should not be given less than 4 hrs. (total: 10 mg.)	10-30 mg. q 6 hrs. (P.O.)	At once	Minutes	3-6 hrs.	Various tachyarrhythmias	S-A, A-V block, CHF, nausea, vomiting, diarrhea, asthma, cardiogenic shock	Erythematous rashes, paresthesias of hands and fever

Key to the table: I-V: intravenous injection; I-M: intramuscular injection; q: every; D/W: dextrose in water; P.O.: orally; hrs.: hours; I-V block: intraventricular block; LE: lupus erythematosus; CHF: congestive heart failure; G-I: gastrointestinal; AF: atrial fibrillation; AFl: atrial flutter; AT: atrial tachycardia; A-V NT: A-V nodal tachycardia; S-V. tachyarrhythmias: supra-ventricular tachyarrhythmias: V. tachyarrhythmias: ventricular tachyarrhythmias.

TABLE VII ANTIBRADYARRHYTHMIC DRUGS

Drugs	Dosage	Onset of Action	Maximum Effect	Duration of Action	Indications	Side Effects and Toxicity
Atropine sulfate	0·3-2 mg. q 4-6 hrs. I-V inj. as needed or the same dose may be given by S-C inj. (total: 4 mg.) or 0·4-0·8 mg. q 4-6 hrs. P.O. for mild form	1-5 min.	Few minutes-30 min.	4-6 hrs.	Primary: Sinus bradycardia, sinus arrest, S-A block Secondary: First degree & occasionally second degree A-V block	Dry mouth, urinary retention, exacerbation of glaucoma, hallucinations, hyperpyrexia, postural hypotension, sinus tachycardia, VPC, ventricular tachycardia
Isoproterenol (Isuprel)	0·02-0·05 mg. (up to 0·1 mg.) I-C or I-V inj., or 0·1-0·4 mg. S-C or I-M inj., q 2-6 hrs. as needed or 1 mg./200 cc. 5% D/W I-V infusion, 1-4 *ug*./min. initially and may increase to 5-10 *ug*/min. as needed. 10-30 mg. sublingually q 1-6 hrs. (for mild cases)	At once Irregular	At once Irregular	Minutes Irregular	Ventricular standstill, severe A-S syndrome Primary: High degree or complete A-V block Secondary: Sinus bradycardia, sinus arrest & S-A block	Tremor, nausea, nervousness, sweating, weakness, dizziness, headache, palpitation, VPC, ventricular tachycardia & fibrillation, hypotension
Epinephrine hydrochloride (Adrenalin)	0·3-0·6 cc. of 1:1000 solution I-V, I-M, S-C or I-C inj., or 0·5-1 mg./250 cc. 5% D/W I-V infusion, 1-4 *ug*./min. initially and may increase to 4-8 *ug*./min. as needed.	At once	At once	Very short	High degree or complete A-V block & ventricular standstill	Trembling, pallor, nervousness, hypertension, VPC, ventricular tachycardia & fibrillation
Ephedrine	30-60 mg. P.O. q 2-4 hrs.	—	—	—	High degree or complete A-V block	Urinary retention, nervousness, vertigo, insomnia, hypertension, ventricular tachyarrhythmias
Corticosteroids	Hydrocortisone I-V inj., 200-600 mg. for 24 hrs. or Solu-Medrol 80 mg. daily by I-M inj., or Prednisone 40-60 mg. daily P.O.	—	—	—	Primary: A-V block with acute onset Secondary: Chronic A-V block	Prolonged steroid therapy may induce sodium retention, Cushing's syndrome, dissemination of TB, aggravation of diabetes mellitus, glaucoma and psychosis
Molar sodium lactate	5-7 cc./kg. I-V infusion over periods of hours. If urgent, 25-50 cc. rapid I-V drip initially	—	—	—	A-V block in the presence of acidosis or hyperkalemia	Precipitation of CHF, alkalosis, hypokalemia, ventricular tachyarrhythmias
Chlorothiazide	0·5-2 gm. daily (P.O.) for 6-8 weeks.	—	—	—	Sinus rhythm with intermittent A-V block	Hypokalemia, precipitation of gout, predispose to digitalis toxicity

Key to the table: q: every; I-V: intravenous; S-C: subcutaneous; I-C: intracardiac; I-M: intramuscular; D/W: dextrose in water; P.O.: by mouth; min.: minute; hrs.: hours; A-S syndrome: Adams-Stokes syndrome; VPC: ventricular premature contraction; TB: tuberculosis; CHF: congestive heart failure.

100 mg. every 2-4 minutes under continuous ECG monitoring. The total intravenous dose should not exceed 2 gm. When the clinical situation is not urgent, Pronestyl may be given orally. Initially, 1 gm. of Pronestyl may be given by mouth to be followed by 0·5 gm. every 2-3 hours as needed. The total oral dose should not exceed 3·5 gm. (Table VI). The usual maintenance dose of Pronestyl is 0·25 to 0·5 gm. every 6 hours by mouth.

The therapeutic effect of Pronestyl is usually observed when the plasma level is 4-8 mg./L. The toxic manifestations of Pronestyl may be observed when the plasma levels exceed 8 mg./L., but toxicity is rare with concentrations of less than 12 mg./L. However, the toxic effects of Pronestyl almost always occur when the concentrations are more than 16 mg./L.

Toxic manifestations of Pronestyl include nausea, vomiting, fever, leukopenia, lymphadenopathy, lupus erythematosus-like syndrome, convulsions, A-V block and intraventricular block of varying degree, ventricular tachyarrhythmias, and hypotension. In some patients who are sensitive to Pronestyl, allergic manifestations such as eosinophilia, urticaria and agranulocytosis may be observed (Table VI).

Lidocaine (Xylocaine)[14-18]

The discovery of the anti-arrhythmic property of lidocaine is probably the most important addition to the therapeutic approach to cardiac arrhythmias. Lidocaine has a similar structure to quinidine or procaine amide, but its electrophysiological properties are quite different. Since lidocaine has little effect on the atria, the drug is of little value in the treatment of atrial tachyarrhythmias. Lidocaine depresses diastolic depolarization and automaticity in the ventricles. It is of interest that lidocaine, in standard doses, has no effect on conduction velocity, and generally shortens both the action potential and the refractory period. Approximately 90% of an administered dose is metabolized in the liver, and the remaining 10% is excreted unchanged via the kidneys. The action of lidocaine is more transient than that of procaine amide and the former penetrates cardiac tissues more rapidly than the latter drug. The onset of action occurs at once following intravenous injection and, the maximum effect is observed shortly thereafter (Table VI).[1] Lidocaine has been widely used, primarily for the treatment of ventricular tacharrhythmias and ventricular premature contractions associated with acute myocardial infarction (Fig. 2), and in cardiac surgery or cardiac catheterization. In the past decade, lidocaine has gradually replaced procaine amide because the former is more effective and seldom produces hypotension when given properly. The secondary indication of lidocaine is in the treatment of various supraventricular tachyarrhythmias when other anti-arrhythmic agents are ineffective. However, the therapeutic result of lidocaine in the treatment of supraventricular tachyarrhythmias is often disappointing.

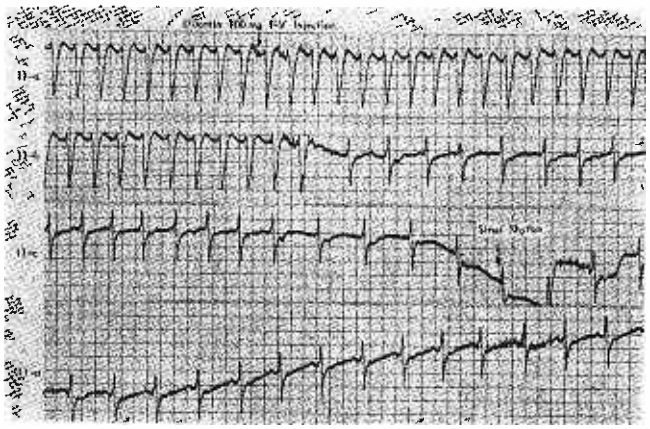

Fig. 4. Leads II-a, b, c and d are continuous. Ventricular tachycardia (rate: 165/min.) induced by digitalis is terminated by Dilantin 100 mg., intravenous injection (indicated by arrow). Note areas of A-V nodal (junctional) tachycardia before a restoration of sinus rhythm. (Reproduced from Edward K. Chung. Digitalis Intoxication. Amsterdam, Excerpta Medica, 1969.)

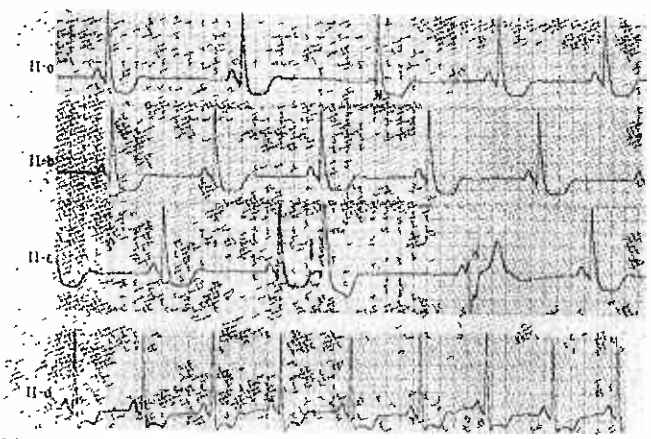

Fig. 5. Leads II-a, b and c are continuous. The rhythm is marked sinus bradycardia (rate: 30-37/min.) with occasional A-V nodal (junctional) and ventricular escape beats (marked N and X) and an atrial premature contraction (indicated by arrow). Lead II-d is taken following intravenous injection of atropine sulfate (0·4 mg.) and the sinus rate is increased (rate: 57/min.) considerably. (Reproduced from Edward K. Chung, Principles of Cardiac Arrhythmias, Baltimore, Williams & Wilkins Co., 1971.)

Tables I-V and Fig. 4. Reproduced from Edward K. Chung, Digitalis Intoxication. Amsterdam, Excerpta Medica, 1969.

Tables VI and VII and Figs. 2 and 5. Reproduced from Edward K. Chung, Principles of Cardiac Arrhythmias, Baltimore, Williams & Wilkins Co., 1971.

For the initiation of therapy, direct intravenous injection of 75 to 100 mg. of lidocaine (1-1·5 mg./Kg.) is given slowly, and the same dose may be repeated every 10 to 20 minutes until ventricular tachyarrhythmias are terminated. In general, the total dose should not exceed 750 mg., and it is advisable that no more than 300 mg. should be administered during a 1-hour period (Table VI). When intravenous injection is not immediately feasible, alternatively, 200 to 250 mg. of lidocaine may be given intramuscularly, and the same dosage may be repeated once or twice every 10 to 20 minutes. It is recommended that lidocaine be administered under continuous electrocardiographic monitoring. Following the termination of the ventricular tachyarrhythmia, continuous intravenous infusion at a rate of 1 to 5 mg./min. is needed for 24 to 72 hours in most cases in order to prevent recurrence of the arrhythmia. When ventricular tachyarrhythmias do not recur, lidocaine may be replaced gradually with oral procaine amide. The oral use of lidocaine in clinical practice needs further investigation.

The therapeutic blood levels of lidocaine are reported to be 1·2-6·0 ug./ml., and blood levels beyond 6·0 ug./ml. occasionally produce toxic manifestations. Significant toxicity is nearly always encountered when the blood level of lidocaine is more than 10 ug./ml.

Lidocaine toxicity is relatively uncommon, but the drug may produce dizziness, drowsiness, confusion, muscle twitching, disorientation, euphoria, cardiac and respiratory depression, convulsions, and hypotension (Table VI). Caution should be employed in the repeated use of lidocaine in patients with severe liver or renal disease because accumulation may lead to toxicity.

Propranolol (Inderal)[19-28]

Propranolol is a beta-adrenergic receptor blocking agent which has been widely used in the management of various tachyarrhythmias, including those induced by digitalis, and those resistant to digitalis. Anti-arrhythmic actions of Inderal are procured by two effects, namely, the inhibition of adrenergic stimulation of the heart, and by a direct action on the electrophysiologic properties of cardiac tissue. Thus, the overall effect of Inderal is a reduction of automaticity, including reduction of the sinus rate, and prolongation of atrial and A-V conduction time.

The onset of action occurs at once following an intravenous injection, and the maximum effect can be reached within minutes (Table VI). Therapeutic effect usually persists for 3 to 6 hours when administered intravenously, as compared to 6-8 hours when administered by mouth (Table VI).

Inderal has been shown to be effective in terminating various tachyarrhythmias. The direct membrane actions of Inderal are primarily responsible for its therapeutic effect in the treatment of digitalis-induced tachyarrhythmias. In addition, Inderal is very effective in the treatment of tachyarrhythmias precipitated by exercise, emotional distress (Fig. 3), or excessive sympathetic stimulation, and supraventricular tachyarrhythmias related to the Wolff-Parkinson-White syndrome. Inderal is contraindicated in patients with bronchial asthma, allergic rhinitis, marked sinus bradycardia, second or third degree A-V block, S-A block, sinus arrest, cardiogenic shock and congestive heart failure.

Inderal should be administered slowly by intravenous injection under ECG monitoring, and the rate of administration should not exceed 1 to 3 mg. per minute. A second dose may be repeated if needed, in 2 minutes. Additional medication should be withheld for at least 4 hours, and the total dose should not exceed 10 mg. (Table VI). In non-urgent situations, Inderal may be given orally in doses ranging between 10 and 30 mg. 3 to 4 times daily before meals and at bedtime. The same dosage schedule is also recommended for long-term use or for prophylactic purposes.

Side effects or toxic manifestations include nausea, vomiting, light-headedness, diarrhea, constipation, mental depression, asthma, hypotension, bradycardia, precipitation of congestive heart failure and cardiogenic shock. In some patients, allergic manifestations such as erythematous rashes, paresthesias of the hands, and fever may be observed (Table VI).

In addition to propranolol, there are new beta-adrenergic blocking agents (Alprenolol, Oxprenolol, and Practolol) which have been used in the treatment of various cardiac arrhythmias with varying success.

Diphenylhydantoin (Dilantin)[2,24,29-32]

The discovery of the anti-arrhythmic properties of Dilantin is another important addition to the management of various cardiac arrhythmias, particularly those induced by digitalis (Fig. 4). Dilantin is similar in structure to the barbiturates, but the electrophysiological properties are quite different from other anti-arrhythmic agents. Conduction velocity in the atria is accelerated by Dilantin resulting from a faster depolarization of the atria. The sinus rate, however, is usually uninfluenced by this drug. Dilantin may accelerate A-V conduction, although A-V conduction may not be influenced by this drug. Intraventricular conduction is not altered significantly by Dilantin as a rule. One of the most important actions of Dilantin is that the drug counteracts the depressant effect on A-V conduction induced by digitalis or procaine amide. In addition, Dilantin depresses diastolic depolarization and automaticity, and shortens the duration of the action potential and the effective refractory period.

The onset of action is immediate (15-45 seconds) following intravenous injection, and the maximum effect is usually reached a few minutes thereafter (Table VI). The duration of action varies, but, in general, it is considered to be between 4 and 8 hours (Table VI). Almost all of the Dilantin administered is hydroxylated in the liver and excreted in the urine.

At present, Dilantin is considered to be the drug of choice in the treatment of various tachyarrhythmias induced by digitalis. This is especially true in the management of digitalis-induced ventricular tachycardia. The secondary indications of Dilantin are as a substitute for Pronestyl or Xylocaine when they are found to be ineffective.

The initial dose of Dilantin is between 125 and 250 mg. given intravenously over 1 to 3 minutes under ECG monitoring. Most patients respond within 3 seconds to 5 minutes. The same dose may be repeated every 10-20 minutes as needed, but the total dose should not exceed 750 mg. per hour (Table VI). Continuous intravenous drip of Dilantin is not practicable because the drug easily precipitates in the various commonly used intravenous solutions. When the situation is not urgent, 200 mg. of Dilantin may be given orally as an initial dose followed by 100 mg. every 4 to 6 hours as needed. Following termination of the tachyarrhythmias, a maintenance dose of 100 mg. 3 to 4 times daily is often needed for varying periods depending upon the clinical situation. Oral Dilantin is often useful in place of Pronestyl or quinidine in long-term therapy. The therapeutic effects usually occur at plasma levels between 10-20 ug./ml.

Toxic manifestations or side effects of Dilantin include respiratory and cardiac depression, skin reactions such as urticaria and purpura, eosinophilia, drowsiness, ataxia, tremor, depression, nervousness, arthralgia, gingival hyperplasia, hypotension, and A-V block of varying degree (Table VI). Fortunately, these manifestations are usually rare.

Bretylium Tosylate[33-35]

Bretylium tosylate (Darenthin) is still a new investigative agent which has been shown to be effective in the treatment of supraventricular as well as ventricular tachyarrhythmias, particularly ventricular fibrillation. This drug is an antiadrenergic agent which blocks postganglionic sympathetic nerve transmission. Bretylium tosylate possesses a positive inotropic action, but significant orthostatic hypotension may be produced because the drug reduces peripheral vascular resistance by its antiadrenergic action.

The recommended intravenous or intramuscular dose of bretylium tosylate is 3-5 mg./Kg. with a maintenance dose of 2-5 mg./Kg. every 8-12 hours. The usual oral doses are 300-600 mg. every 8 to 12 hours.

Potassium[2,24]

Potassium is probably one of the most effective agents in abolishing various tachyarrhythmias in digitalis intoxication. The amount of potassium administration depends upon the severity of the toxicity, degree of suspected potassium deficiency in the myocardium and the response to potassium therapy. Potassium is definitely contraindicated in the presence of renal failure and hyperkalemia. Potassium is also relatively contraindicated in the presence of second degree or complete A-V block unless the serum potassium is proved to be very low.

For mild toxicity of digitalis, potassium chloride can be given orally in doses of 1 to 2 gm. every 4-6 hours. For severe toxicity, 40 to 60 mEq./L. of potassium chloride, diluted in 500 cc. of 5% dextrose in water, may be administered by slow intravenous infusion over a one to 3 hour period under ECG monitoring. Frequent determinations of serum potassium are also indicated.

Anti-Bradyarrhythmic Agents

Because of the ready availability of artificial pacemakers, various anti-bradyarrhythmic agents are now much less commonly used than in the past decade. Nevertheless, these agents are valuable for the management of milder forms of slow rhythms such as marked sinus bradycardia, sino-atrial block, etc. In addition, anti-bradyarrhythmic agents are extremely useful in urgent situations such as in the Adams-Stokes syndrome, when artificial pacemakers are not immediately available. Various anti-bradyarrhythmic agents are listed in Table VII, but among them, atropine sulfate and isoproterenol are probably most commonly used drugs.

Atropine[24,36-38]

Atropine is primarily used to accelerate the sinus rate by vagal inhibition. Thus, this is the drug of choice for marked symptomatic sinus bradycardia (Fig. 5). Atropine is also effective in the treatment of sinus arrest or sinoatrial block. A secondary indication for atropine is in the treatment of first or second degree A-V block (usually Wenckebach type) especially in acute diaphragmatic myocardial infarction, or digitalis toxicity. Atropine is usually not effective in the treatment of high degree or complete A-V block. The onset of action occurs within 1-5 minutes after injection, and the maximum effects are observed within a few to 30 minutes thereafter. The duration of action usually lasts 4-6 hours.

Atropine is best administered intravenously in a dosage between 0·3 and 1 mg. (up to 2·0 mg.), and a similar dosage may be repeated every 4 to 6 hours as needed. The total dosage of atropine should not exceed 4 mg. (Table VII). The effect of the drug is usually prompt. Atropine may be given subcutaneously if the intravenous route is not feasible

immediately. Oral administration of atropine has been used but its effectiveness is less predictable.

Serious toxic effects of atropine are uncommon, but ventricular premature contractions or ventricular tachyarrhythmias may be induced. Common side effects, or mild toxicity, include a dry mouth, urinary retention, exacerbation of glaucoma, halucinations, hyperpyrexia and marked sinus tachycardia (Table VII).

Isoproterenol (Isuprel)[24,37-41]

Before artificial pacemakers were available for clinical use, the treatment of choice for complete A-V block was the administration of Isuprel. The drug is still very useful in the treatment of Adams-Stokes syndrome in an emergency, or temporarily until an artificial pacemaker can be inserted. Thus, Isuprel is, at present, still the drug of choice in the treatment of the Adams-Stokes syndrome due to bradyarrhythmias, primarily complete A-V block. Isuprel is capable of accelerating both the supraventricular and the ventricular pacemakers and of improving A-V conduction. The drug possesses a potent inotropic action leading to an increment in the stroke volume, the amplitude of myocardial contraction and the coronary blood flow. The onset of action is immediate following injection and the maximum effect is also observed almost instantaneously (Table VII). Consequently, the duration of action only lasts a few minutes unless it is administered by continuous intravenous infusion.

The primary indication of Isuprel is in the treatment of the Adams-Stokes syndrome due to complete A-V block, or ventricular standstill until an artificial pacemaker is inserted. Its secondary indication is in place of atropine, in the treatment of symptomatic sinus bradycardia, sinus arrest, and S-A block.

Isuprel can be given by direct intracardiac (I-C), intravenous (I-V), intramuscular (I-M) or subcutaneous (S-C) injection, or it may be given by intravenous infusion.

In emergency situations, such as in severe Adams-Stokes syndrome or ventricular standstill, Isuprel can be given by intracardiac or intravenous injection. The usual dosage is between 0·02 and 0·05 mg., but up to 0·1 mg. may be administered. Otherwise, the drug can be given subcutaneously or intramuscularly in a dosage of 0·1 to 0·4 mg. every 2-6 hours as needed. In addition, continuous intravenous infusion of Isuprel is indicated in severe cases in order to maintain the ventricular rate around 50-60 beats per minute until an artificial pacemaker can be inserted. The usual method is to dilute 0·1 mg. of Isuprel in 200 cc. of 5% dextrose in water, and the initial infusion rate is 1 to 4 ug. per minute. The infusion rate may be increased to 5 to 10 ug. per minute, and, occasionally, up to 40 ug. per minute may be required to maintain an acceptable ventricular rate (Table VII).

The most popular route for this drug is sublingually, and the usual dosage is 10 to 30 mg. every 1 to 6 hours. Occasionally, the drug can be given as often as every 30 minutes as needed.

Side effects or mild toxicity of Isuprel include tremor, nervousness, sweating, nausea, weakness, headache, dizziness, palpitation and hypotension (Table VII). A serious toxic effect is the production of ventricular tachyarrhythmias which may occur with either small or large doses.

Epinephrine Hydrochloride (Adrenalin)[24,38,42]

Adrenalin has been almost as popular as Isuprel in the treatment of the Adams-Stokes syndrome. However, Adrenalin is considered to be definitely inferior to Isuprel because the former drug produces significant hypertension and is prone to provoke ventricular irritability, particularly ventricular fibrillation.

Adrenalin is capable of accelerating the atrial rate as well as the ventricular rate. The degree of acceleration of the atrial rate has no relationship to the initial atrial rate, whereas the degree of the acceleration of the idioventricular rate is closely related to the initial ventricular rate. Thus, the degree of acceleration of the idioventricular rate is greatest when the initial ventricular rate is very slow, while the enhancement of the ventricular rate is insignificant when the inital ventricular rate is relatively rapid.

The onset of action and the maximum effect are observed immediately after injection, and the duration of action is very short.

The primary indication of Adrenalin is in the treatment of ventricular standstill, particularly when associated with acute myocardial infarction. The secondary indication for Adrenalin is in the treatment of the Adams-Stokes syndrome due to complete A-V block until an artificial pacemaker is inserted. In urgent situations, as in ventricular standstill, Adrenalin 0·3 to 0·6 cc. of 1:1000 solution may be given by intravenous (I-V), intramuscular (I-M), subcutaneous (S-C) or even intracardiac (I-C) injection. Slow injection over a period of several minutes is recommended under ECG monitoring and the rate of injection should be regulated according to the patient's response (Table VII). For long-term therapy, 0·5 to 1 mg., 1:1000 solution of Adrenalin diluted in 250 cc. of 5% dextrose in water can be given by a continuous intravenous infusion. The initial rate of the intravenous drip is usually 1 ro 4 ug. per minute, and the rate may be increased to 4 to 8 ug. per minute according to the patient's response (Table VII).

Side effects or mild toxicity of epinephrine include nervousness, trembling, pallor and hypertension. A serious toxic effect is the production of ventricular tachycardia and fibrillation. The usefulness of epinephrine in the treatment of the Adams-Stokes syndrome is limited because of its serious toxic effects, and its ineffectiveness in some cases.

Miscellaneous Agents

Detailed information regarding other anti-bradyarrhythmic drugs including ephedrine, corticosteroids, molar sodium lactate and chlorothiazide is described in Table VII.

SUMMARY

The best therapeutic results only follow a correct and precise diagnosis of the cardiac arrhythmia. In addition, the proper agent should be administered according to the underlying etiological factor.

Various pharmacologic agents are essential in terminating ectopic tachyarrhythmias. Furthermore, some drugs, particularly quinidine and Pronestyl, must be used for long-term therapy in preventing various arrhythmias. In refractory arrhythmias, anti-arrhythmic agents are often used in conjunction with direct current shock and/or an artificial pacemaker.

Serious side effects or toxicity of various anti-arrhythmic agents should not be dismissed lightly. Careful consideration of indications, contraindications, proper dosage, interrelationships between various drugs, in addition to the correct diagnosis of arrhythmias can achieve the best therapeutic result, and may minimize or even avoid serious side effects or toxicity.

REFERENCES

1. Withering, W.: "An Account of the Foxglove and some of its Medical uses with Practical remarks on Dropsy and other Diseases." M. Swinney, London, 1785.
2. Chung, E. K.: "Digitalis Intoxication, Amsterdam, Excerpta Medica." 1969.
3. Smith, T. W. and Haber, E.: "Digoxin intoxication: The relationship of clinical presentation to serum digoxin concentration." J. Clin. Invest., 49, 2377, 1970.
4. Hillestad, L., Bjerkelund, C., Dale, J., Maltau, J. and Storstein, O.: "Quinidine in maintenance of sinus rhythm after electroconversion of chronic atrial fibrillation. A controlled clinical study." Brit. Heart J., 33, 518, 1971.
5. Bloomfield, S. S., Romhilt, D. W., Chou, T. C. and Fowler, N. O.: "Quinidine for prophylaxis of arrhythmias in acute myocardial infarction." New Engl. J. Med., 285, 979, 1971.
6. Stern, S.: "Treatment and prevention of cardiac arrhythmias with propranolol and quinidine." Brit. Heart J., 33, 522, 1971.
7. Hartel, G., Louhija, A., Konttinen, A. and Halonen, P. I.: "Value of quinidine in maintenance of sinus rhythm after electric conversion of atrial fibrillation." Brit. Heart J., 32, 57, 1970.
8. Luchi, R. J., Helwig, J., Jr. and Conn, H. L.: "Quinidine toxicity." Am. Hear. J., 65, 340, 1963.
9. Bigger, J. T. and Heissenbuttel, R. H.: "The use of procaine amide and lidocaine in the treatment of cardiac arrhythmias." Prog. Cardiovas. Dis., 11, 515, 1969.
10. Koch-Weser, J. and Klein, S. W.: "Procainamide dosage schedules, plasma concentrations and clinical effects." J.A.M.A. 215, 1454, 1971.

11. Dubois, E. L.: "Procainamide induction of a systemic lupus erythematosus-like syndrome." Medicine, 48, 217, 1969.
12. Harrison, D. C., Sprouse, J. H. and Morrow, A. G.: "The antiarrhythmic properties of lidocaine and procaine amide." Circulation, 28, 486, 1963.
13. Paine, R.: "Procainamide hydrochloride and lupus erythematosus." J.A.M.A., 194, 23, 1965.
14. Gianelly, R., Von Der Groeben, J. O., Spivack, A. P. and Harrison, D. C.: "Effect of lidocaine on ventricular arrhythmias in patients with coronary heart disease." New Engl. J. Med., 277, 1215, 1967.
15. Malach, M., Kostis, J. B. and Fischetti, J. L.: "Lidocaine for ventricular arrhythmias in acute myocardial infarction." Am. J. Med. Sci., 257, 52, 1969.
16. Grossman, J. I., Lubow, L. A., Frieden, J. and Rubin, I. L.: "Lidocaine in cardiac arrhythmias." Arch. Int. Med., 121, 396, 1968.
17. Bernstein, V., Bernstein, M., Griffiths, J. and Peretz, D. I.: "Lidocaine intramuscularly in acute myocardial infarction." J.A.M.A., 219, 1027, 1972.
18. Chopra, M. P., Thadani, U., Portal, R. W. and Aber, C. P.: "Lidocaine therapy for ventricular ectopic activity after acute myocardial infarction: A double-blind trial." Brit. Med. J., 3, 668, 1971.
19. Lucchest, B. R. and Whitsitt, L. S.: "The pharmacology of beta-adrenergic blocking agents." Prog. Cardiovas. Dis., 11, 410, 1969.
20. Gibson, D. and Sowton, E.: "The use of beta-adrenergic receptor blocking drugs in dysrhythmias." Prog. Cardiovas. D., 12, 16, 1969.
21. Frieden, J., Rosenblum, R., Enselberg, C. D. and Rosenberg, A.: "Propranolol treatment of chronic intractable supraventricular arrhythmias." Am. J. Cardiol., 22, 711, 1968.
22. Levi, G. F. and Proto, C.: "Combined treatment of atrial fibrillation with propranolol and quinidine." Cardiology, 55, 249, 1970.
23. Fors, W. J., Jr., Vanderark, C. R. and Reynolds, E. W., Jr.: "Evaluation of propranolol and quinidine in the treatment of quinidine-resistant arrhythmias." Am. J. Cardiol., 27, 190, 1971.
24. Chung, E. K.: "Principles of Cardiac Arrhythmias." Baltimore, Williams and Wilkins Co., 1971.
25. Norris, R. M.: "Alprenolol in acute myocardial infarction: Double-blind trial." New Zealand Med. J., 71, 135, 1970.
26. Sandler, G. and Pistevos, A. C.: "Use of oxprenolol in cardiac arrhythmias associated with acute myocardial infarction." Brit. Med. J., 1, 254, 1971.
27. Kerber, R. E., Goldman, R. H., Gianelly, R. E. and Harrison, D. C.: "Treatment of atrial arrhythmias with alprenolol." J.A.M.A., 214, 1849, 1970.
28. Gibson, D. G. and Coltart, D. J.: "Haemodynamic effects of practolol." Brit. Heart J., 34, 95, 1972.
29. Damato, A. N.: "Diphenylhydantoin: Pharmacological and clinical use." Prog. Cardiovas. Dis., 12, 1, 1969.
30. Bigger, J. T., Schmidt, D. H. and Kutt, H.: "Relationship between the plasma level of diphenylhydantoin sodium and its cardiac antiarrhythmic effects." Circulation, 38, 363, 1968.
31. Rosen, M., Lisak, R. and Rubin, I. L.: "Diphenylhydantoin in cardiac arrhythmias." Am. J. Cardiol., 20, 674, 1967.
32. Bashour, F. A., Edmonson, R. E. Gupta, D. N. and Prati, R.: "Treatment of digitalis toxicity by diphynylhydantoin (Dilantin)." D. Chest, 53, 263, 1968.
33. Taylor, S. H., Saxton, C. Davies, P. S. and Stoker, J. B.: "Bretylium tosylate in prevention of cardiac dysrhythmias after myocardial infarction." Brit. Heart J., 32, 326, 1970.
34. Day, H. W. and Bacaner, M.: "Use of bretylium tosylate in the management of acute myocardial infarction." Am. J. Cardiol., 27, 177, 1971.
35. Bernstein, J. G. and Koch-Wester, J.: "Effectiveness of bretylium tosylate against refractory ventricular arrhythmias." Circulation, 45, 1024, 1972.
36. Fowler, N. O.: "Sinus bradycardia and sinus tachycardia. In Modern Treatment." Edited by N. O. Fowler, New York, Harper and Row, 1970.
37. Adolph, R. J.: "Treatment of atrioventricular block." In Modern Treatment. Edited by N. O. Fowler, New York, Harper and Row, 1970.
38. Vogel, J. H. K. and Brammel, H. L.: "Pharmacologic therapy of A-V block." In Mechanisms and Therapy of Cardiac Arrhythmias. Edited by L. S. Dreifus and W. Likoff. New York, Grune and Stratton, Inc., 1966.
39. Bluestone, R. and Harris, A.: "Treatment of heart block with long-acting isoprenaline." Lancet, 1, 1299, 1965.
40. Vogel, J. H. K.: "Use of isoproterenol in the treatment of complete heart block complicating acute myocardial infarction." Am. J. Cardiol., 7, 746, 1961.
41. Chandler, D. and Clapper, M. I.: "Complete atrioventricular block treated with isoproterenol hydrochloride." Am. J. Cardiol., 3, 336, 1959.
42. Robbin, S. R., Goldfein, S., Schwartz, M. J. and Dack, S.: "Adams-Stokes syndrome." Am. J. Med., 18, 577, 1955.

PATHOGENESIS OF BRADY AND TACHYARRHYTHMIAS

By Yoshio Watanabe

Cardiac rhythm disturbances with either slow or rapid ventricular rates result from several different mechanisms. Clinically, bradyarrhythmias may be classified into sinus bradycardia, sinus arrest and sick sinus syndrome, sinoatrial or intraatrial block, atrioventricular block (type A or B), exit block from an ectopic pacemaker, nonconducted atrial premature systoles, and malfunctioning of electronic pacemaker with failure of ventricular capture. In contrast, tachyarrhythmias are subdivided into sinus tachycardia, paroxysmal and nonparoxysmal supraventricular tachycardias (either atrial or A-V junctional), atrial flutter and fibrillation, paroxysmal and nonparoxysmal ventricular tachycardial, ventricular fibrillation, W-P-W tachycardia and malfunctioning electronic pacemaker with competition of intrinsic and electronic stimuli.

Electrophysiologically, on the other hand, the genesis of most cardiac arrhythmias is usually explained by (1) either depressed or enhanced automaticity, (2) simple conduction block, (3) unidirectional block and re-entry, or (4) various combinations of these mechanisms. In this paper, an attempt will be made to correlate the clinical varieties of brady-and tachyarrhythmias with these electrophysiological derangements, and some of the common factors producing these electrophysiological alterations are also discussed.