CARDIOVASCULAR DRUG THERAPY

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Cardiovascular Drug Therapy

Preface

Over the past few years a large number of new drugs have become available in the therapeutic armamentarium for clinicians to treat patients with cardiovascular diseases. Not only have more drugs been added to those with similar mechanisms of action but entirely new classes of compounds are now available with exciting and novel activities. This includes development of drugs that combine more than one class of action, which brings exciting new possibilities to therapeutics that are quite distinct from those agents in the past that represented two drugs combined physically within the same capsule.

This book has a purpose. It is to provide updated information concerning the availability of new agents and a comparative evaluation of their uses, limitations, and efficacy. The subjects covered include the antiarrhythmic drugs for the treatment of ventricular arrhythmias with the hope of preventing sudden cardiac death, drugs for the treatment of congestive heart failure (the inotropes, vasodilators, and diuretics) and classes of drugs known as the beta-adrenergic and alpha-adrenergic blocking drugs, which have uses in the treatment of patients who have hypertensive, ischemic, and arrhythmic disorders. Finally, drugs to treat hypertension, which also include an introduction to the newest agents, called ACE inhibitors and calcium channel blockers, are discussed.

With the advent of noninvasive technology to identify patients at high risk of sudden cardiac death, and advances in the technology to simply define the frequency and severity of ventricular arrhythmias (which are the two key risk factors), the antiarrhythmic drug field has become much more important. This is evidenced by the tremendous degree of activity in the pharmaceutical industry in the development of new and different types of antiarrhythmic agents. Before 1980 there were only three oral antiarrhythmic agents (quinidine, procainamide, and disopyramide) available in the United States. In the 1980s we expect at least six new agents to be available and there are many more undergoing early phases of clinical investigation. The chapter entitled "Antiarrhythmic Drugs" has been orga-

nized using the Vaughan Williams Classification System as a means to provide comparative efficacy and tolerance data. While there is an electrophysiologic basis for this classification, unfortunately some of the antiarrhythmic drugs currently under study and those to come do not fit neatly into such a system. Nevertheless, it does provide a framework for comparison and contrasts. Drugs that have been released by the Food and Drug Administration are presented first in the chapter, followed by the experimental agents.

Chapters 2 and 3, on beta- and alpha-adrenergic blocking drugs, are presented in a slightly different format than the former chapter, which cover details of specific drugs. With the discovery that beta-adrenergic blocking agents have such important uses in the various clinical syndromes in cardiovascular medicine and that many of their differences can be presented in terms of pharmacologic principles and structure activity relationships (selectivity, membrane stabilizing activity, and intrinsic sympathomimetic activity), the primary presentation of these chapters relates to mechanisms of action and general class considerations. Alpha-adrenergic blocking agents likewise are discussed from a physiologic point of view, and the drug effects in various clinical states are highlighted, rather than separated, by individual drugs.

Agents for the treatment of patients with left ventricular dysfunction include inotropes, vasodilators, and diuretics. The incidence of chronic congestive heart failure has increased in terms of its recognition in the last decade and it now is the leading cause of death from heart disease in hospitalized patients. Advances in the therapy of heart failure have become important to the clinician and are based on physiologic principles of cardiac mechanics and metabolic consequences. Oral inotropic agents, ACE inhibitors, vasodilators, and a discussion of the proper role of diuretics are all addressed in this chapter.

Antihypertensive drugs are, of course, extremely important since hypertension is such a common disorder, and data are now clear that therapy is indicated early in its natural history. A complete discussion of the antihypertensive drugs including diuretics, beta-blocker drugs, alpha-adrenergic drugs, vasodilators, and ACE inhibitors is presented in the final chapter with specific clinical indications, interactions, and physiologic discussion. Finally, the pharmacophysiology and clinical indications of calcium channel blockers in their potential role as antihypertensive drugs are addressed.

It is hoped that this book will provide the reader with a basis for the comparative use and safety of drugs for the treatment of cardiovascular disorders.

THE AUTHORS

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Chapter 1

Antiarrhythmic Drugs

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DURING THE PAST DECADE, quinidine, procainamide, disopyramide, and lidocaine have formed the available antiarrhythmic armamentarium. During this time, several new antiarrhythmic drugs have been evaluated and recently released for general use. These agents, mexiletine, tocainide, flecainide, and amiodarone, will significantly increase our ability to control arrhythmias. Pharmaceutical development continues, and several new and promising agents are presently under investigation. Although these drugs share several common features, significant differences exist in their electrophysiologic and hemodynamic effects, pharmacokinetic properties, and efficacy for certain arrhythmias. The various aspects of each drug will be discussed in this chapter.

There are a variety of classification schema that have been applied to antiarrhythmic drugs. We have elected to use the Harrison modification[133a] of the Vaughn Williams classification in the present chapter.[383] In this schema, antiarrhythmic drugs are classified based on their in vitro electrophysiologic effects. Agents that decrease the upstroke velocity of the action potential and thus slow conduction are classified as class I. Within class I, subclassifications are made into classes IA, IB, and IC based upon whether the depression of conduction is moderate, weak, or strong, respectively. Class III antiarrhythmic agents are those with prolonged refractoriness. Classes II and IV antiarrhythmic agents are β-adrenergic and calcium-channel blocking agents, respectively. They will be discussed in other sections of this book.

Several antiarrhythmic drugs in addition to having antiarrhythmic effects have other pharmacologic properties. Amiodarone, sotalol, and bretylium possess adrenergic blocking effects, and propafenone has both β-adrenergic and calcium-channel blocking activities. These properties

will be discussed to the extent that they are understood and are significant.

Because the clinician is faced with a choice between individual agents of differing properties, a comparison of agents is useful. Thus, whenever possible, direct comparisons between agents will be made to enable appropriate selection of antiarrhythmic agents for specific arrhythmias. Since the selection of an antiarrhythmic agent requires not only an understanding of the drug's efficacy but also its metabolism, toxicity, and hemodynamic effects, these effects will be emphasized. In addition, the agents will be grouped into two categories: those that are approved for use in the United States and those that remain under investigation in this country.

QUINIDINE

Quinidine is the oldest antiarrhythmic agent currently in use and is one of the most frequently used agents for the treatment of both supraventricular and ventricular arrhythmias. Quinidine, the *d*-isomer of quinine, is a cinchona derivative. Cinchona derivatives were used in the treatment of cardiac arrhythmias in the eighteenth century and were reported for this purpose by Heyninger and Pasteur.[403] The use of quinidine for the treatment of arrhythmias became popular after the report of Frey.[112] The early use of quinidine is well summarized in a review by Sokolow.[356]

Electrophysiology

Quinidine has both direct and indirect (anticholinergic) effects on cardiac electrophysiology. Through its local anesthetic action, quinidine decreases the responsiveness of cardiac cells. It decreases the maximum rate of depolarization (phase 0 of the action potential) and thus conduction velocity and the amplitude of the action potential in atrial, ventricular, and Purkinje tissue.[143] Excitability is also depressed. Quinidine, in addition, delays repolarization, thus prolonging the action potential duration and increasing dispersion of refractoriness in myocardial fibers.[396] Quinidine depresses normal and abnormal automaticity by decreasing the slope of phase 4 depolarization; however, in very high concentrations, quinidine can cause abnormal automatic firing in specialized conduction fibers.[143] In vitro, high concentrations of quinidine have been shown to depress sinus node function; however, little or no effect on sinus node automaticity is seen clinically.[143, 231]

Quinidine produces significant anticholinergic effects and particularly when administered intravenously can produce reflex sympathetic responses that result from α-adrenergic blockade.[244]

Quinidine produces electrocardiographic changes that are the result of its electrophysiologic effects. It has little effect on sinus rate. QRS duration is increased as a result of conduction slowing in the specialized conduction system and ventricular muscle. Prolongation of the PR and QRS intervals, however, are typically modest. The JT interval increases as a result of the prolongation of the action potential.

Hemodynamics

Early studies in animals suggested that intravenous doses of quinidine produced marked depression of myocardial contractility.[294] More recent studies in conscious animals have shown little effect on left ventricular contractile function.[389] Chronic oral quinidine administration in doses that produce plasma concentrations that are typically achieved clinically (2 to 8 μg/ml) produced no significant depression of left ventricular function during rest or the stress of a pressure load.[276] Thus, in the experimental animals, quinidine produces little significant depression of left ventricular function. Neither intravenous nor oral quinidine has been shown to adversely affect left ventricular contractile function in normal volunteers or patients with congestive cardiomyopathy and significant left ventricular dysfunction.[77, 230]

Quinidine produces significant peripheral vasodilatation as a result of its direct smooth muscle relaxing effect as well as its α-adrenergic blocking properties.[268, 331] Because of these effects, quinidine when administered intravenously can produce significant hypotension. Little if any clinically significant hemodynamic effects have been reported with oral quinidine.

Pharmacokinetics

After oral administration, 90% of the dose of quinidine is available to the systemic circulation. Plasma concentrations peak at 60 to 90 minutes after administration of the sulfate salt and slightly later following administration of the gluconate salt.[74] Quinidine is highly protein bound (approximately 80%). Since it is the unbound or free concentration of the drug that is available for diffusion across all membranes, this is the portion that is active. Several metabolites of quinidine have been identified and some may be pharmacologically active.[146]

Quinidine is eliminated primarily by hepatic degradation. Renal clearance of unmetabolized quinidine accounts for less than 10% of quinidine elimination. Thus, it is generally not necessary to alter quinidine dosing regimens in patients with impaired renal function. On the other hand, plasma quinidine concentrations are elevated in patients with liver dys-

function or congestive heart failure because of hepatic dysfunction and reduction in hepatic blood flow. Particular care must be taken in administering quinidine to such patients.[74, 93, 179] Because of the wide interpatient variability in the extent of metabolism and other factors previously discussed, there is a large interpatient variability in the relationship between quinidine dose and the resultant plasma concentration.

Preparations and Administration

Quinidine is available in both oral and parenteral forms. The parenteral (usually intravenous) form is the gluconate salt. It is administered in a dose of 200 to 400 mg at a rate of 10 mg/min.

The oral preparation of quinidine is available as sulfate, gluconate, or polygalacturonate salts. A variety of preparations of these salts are available. The dosage required for efficacy varies widely. Typical oral quinidine dosing is achieved with approximately 15 mg/kg of quinidine base administered over 24 hours. The specific dose and dosing interval depend upon the preparation selected. Quinidine sulfate is typically administered in a dose of 200 to 600 mg every 6 hours. Newer sustained released preparations of the sulfate salt may require less frequent administration. The gluconate salt of quinidine is more slowly absorbed and has a longer half-life, thus it may be administered every 8 to 12 hours. Loading doses are generally not recommended using the oral preparation.

Quinidine administration is monitored by observation of the electrocardiographic intervals and cardiac and noncardiac side effects. In certain patients, monitoring plasma concentrations may be helpful. In patients with normal QRS- and JT-interval durations prior to quinidine therapy, increases in these intervals of 25% to 50% may be acceptable. If these intervals are abnormal prior to quinidine administration, an increase of 25% is the typical maximum acceptable. Monitoring of quinidine plasma concentrations can be useful because of the wide interpatient variability in achieved plasma concentrations. Generally, a concentration of 1.5 to 4 μg/ml at the trough level is considered acceptable. Adverse effects become more common as plasma concentrations exceed 4 μg/ml, and an extremely high incidence of toxicity has been noted at levels above 7 μg/ml.

Efficacy

Quinidine is useful in the therapy of both supraventricular and ventricular arrhythmias. Its major uses have been for the maintenance of sinus rhythm after conversion of atrial flutter or fibrillation, prevention of paroxysmal supraventricular tachycardia, and the suppression of ventricular premature complexes and ventricular tachyarrhythmias.

Supraventricular Arrhythmias

Since the advent of electrical cardioversion, quinidine has not been frequently used for the conversion of supraventricular tachyarrhythmias, particularly atrial fibrillation, to sinus rhythm. Quinidine, however, remains the drug of choice for maintenance of sinus rhythm following conversion of atrial fibrillation.[36, 355] Quinidine is also useful in the prophylactic treatment of paroxysmal supraventricular tachycardia, particularly with the adjunctive use of a β-blocking agent.

Ventricular Arrhythmias

Quinidine has been reported in older literature to be effective in adequately suppressing ventricular arrhythmias in 80% to 90% of patients.[356] In more recent studies utilizing modern techniques and objective indices of efficacy, suppression of ventricular premature complexes has been reported in 60% to 80% of patients.[279] In these studies, quinidine sulfate was used in doses between 800 and 1,800 mg/day and plasma concentrations of 2 to 3 μg/ml were achieved. In one typical study of 20 patients with ventricular premature complexes studied in a double-blind trial comparing quinidine with placebo, a significant reduction in ventricular premature complexes was noted in 70% of patients in a short-term (4-day) trial and 60% of patients in a long-term (8-week) trial.[279] These more recent trials have used Holter monitoring techniques to identify significant antiarrhythmic effects.

Quinidine has also been used to treat ventricular premature complexes following acute myocardial infarction. Although not commonly used for this purpose now, quinidine in doses of 300 to 400 mg every 6 to 8 hours is effective when compared with placebo in suppressing ventricular premature complexes and ventricular tachycardia in the acute infarction setting.[34, 162]

Quinidine has also been evaluated utilizing invasive electrophysiologic studies in patients with life-threatening ventricular tachyarrhythmias. In this testing model, arrhythmias that were inducible by programmed electrical stimulation during baseline studies could no longer be induced in 30% to 40% of patients during chronic quinidine therapy.[89, 296] The plasma concentrations of quinidine that produce these effects generally range from 2 to 4 μg/ml.

Adverse Effects

The primary adverse effects of quinidine are gastrointestinal. Nausea, vomiting, and diarrhea are the most common side effects. These can re-

quire alteration in dose or discontinuation of quinidine in 10% to 20% of patients. Cinchonism (tinnitus, reduced aural acuity, blurred vision, and gastrointestinal upset) is a classic although not commonly seen form of quinidine toxicity. Hypersensitivity reactions to quinidine include fever and rashes although these are not common. Thrombocytopenia is also an uncommon adverse reaction that can occur several weeks to months after starting quinidine therapy. The observation of petechiae following the institution of quinidine therapy warrants a hematologic investigation.

The worsening of an already existing ventricular arrhythmia or the production of a new ventricular arrhythmia is a well-reported adverse effect of all antiarrhythmic therapy.[384] The actual incidence of this complication of quinidine therapy is not known; however, it is thought to be relatively rare. An increase in the frequency of ventricular premature complexes has been reported to occur following initiation of quinidine therapy in 10% to 15% of patients. This is generally asymptomatic and of uncertain clinical significance. On the other hand, life-threatening ventricular tachyarrhythmias such as torsades de pointes may also occur following the initiation of quinidine therapy; however, the incidence of this adverse effect is probably less than 1%.[109, 279, 384] This latter complication, the provocation of torsades de pointes, is typically seen in patients with marked QT prolongation and is usually associated with hypokalemia and bradycardia. Careful monitoring of the electrocardiogram to identify marked QT prolongation and avoidance of hypokalemia can reduce this potentially life-threatening adverse effect.

Drug Interactions

Several significant drug interactions involving quinidine have been described. During coadministration of quinidine and digoxin, significant increases in digoxin plasma concentrations have been reported.[207] This interaction is frequently clinically significant. Digoxin doses should be decreased by approximately 50% when quinidine is added to a stable regimen.

Quinidine elimination can be significantly affected by drugs that induce hepatic enzymes such as phenobarbital and phenytoin. Monitoring of plasma concentrations during initiation of therapy with such agents is important because increased rates of quinidine elimination can be expected during concomitant administration of such drugs.

Although uncommon, quinidine may potentiate the anticoagulant effect of warfarin, and close monitoring of prothrombin times after initiation of quinidine therapy in anticoagulated patients is recommended.[189]

Summary

Quinidine is a class IA antiarrhythmic agent that is effective in the treatment of both supraventricular and ventricular arrhythmias. It slows conduction to a moderate degree in most myocardial tissue and has little or no effect on sinus node function. Its administration generally does not produce clinically significant hemodynamic alterations. It is effective in suppressing ventricular premature complexes in 50% to 70% of patients and has been shown to be effective in approximately one third of patients with life-threatening ventricular tachyarrhythmias evaluated with electrophysiologic testing. Its principal toxicity is gastrointestinal, and reduction in dosing or discontinuation of the agent is necessary in 15% to 30% of patients because of adverse effects.

PROCAINAMIDE

Procainamide was developed following studies that showed that procaine, an anesthetic agent, increased the stimulation threshold of the ventricles.[232] The clinical utility of procainamide was reported in 1951 and a comprehensive review of its early use followed 10 years later.[173, 226]

Electrophysiology

The electrophysiologic effects are similar to those of quinidine.[143] Procainamide reduces the rate of depolarization of atrial, ventricular, and Purkinje tissues and thus reduces conduction velocity in these tissues. It reduces excitability and prolongs repolarization. Procainamide has a more potent effect on partially depolarized and electrophysiologically abnormal cells than on normal cells.[143] Procainamide, like most antiarrhythmic agents, depresses the slope of phase 4 depolarization and thus depresses automaticity.

The electrocardiographic effects of procainamide reflect its electrophysiologic effects. Procainamide increases the QRS duration and prolongs the JT interval. Guidelines for its use are similar to those employed for quinidine.

Hemodynamics

Procainamide produces hypotension when it is administered intravenously. This hypotension is dependent on the dose and rate of administra-

tion. When more than 750 mg of procainamide is administered intravenously, some change in the blood pressure generally occurs. Typical dosing regimens, however, allow administration of between 1,000 and 2,000 mg of procainamide in most patients without severe hemodynamic consequences. Procainamide produces hypotension by both peripheral vasodilatation and depression of myocardial contractility. Depression of ventricular contractility is dose related and is generally seen only with intravenous therapy. In individual patients with left ventricular dysfunction, however, significant effects on ventricular contractility even with oral dosing have been reported.[47, 134]

Pharmacokinetics

Procainamide is well absorbed after oral administration and has a bioavailability of greater than 75%. The binding of procainamide to plasma proteins is negligible and generally does not exceed 15% to 20%.

Procainamide is eliminated by both hepatic metabolism and renal excretion. Its major metabolite is N-acetyl procainamide (NAPA). The rate of conversion of procainamide to NAPA varies significantly among patients and accounts for a substantial interpatient variability in the level of procainamide present in the serum following administration of a standard dose of the agent. NAPA is known to have antiarrhythmic activity and a somewhat longer half-life (4 to 6 hours) than procainamide (3 to 4 hours).

Unaltered procainamide and NAPA are excreted by the kidneys. Procainamide excretion is reduced in patients with significant renal insufficiency. Furthermore, the excretion of procainamide can be reduced in patients with depressed cardiac function, and a reduction in dose in such patients is recommended. Marked accumulation of NAPA can also be noted in patients with congestive heart failure and renal insufficiency. If possible, the use of procainamide should be avoided in patients with severe renal impairment.

The significance of NAPA in the pharmacokinetics of orally administered procainamide has been emphasized. NAPA does not appear to have an effect in the production of antinuclear antibodies or the lupus syndrome, which can be seen during procainamide therapy. However, many of the gastrointestinal adverse effects of procainamide may be related to NAPA.[307]

Preparations and Administration

Procainamide is available in both intravenous and oral preparations. Intravenous procainamide should be administered at a dose of 25 to 50 mg/min until the arrhythmia is suppressed or a maximum of 1,000 to 2,000 mg

has been reached. Generally, a dose of 15 to 25 mg/kg is the desired loading dose. Maintenance infusions of 2 to 6 mg/min can be used to maintain adequate plasma levels.

Oral procainamide is available as the hydrochloride salt in capsules. This form is infrequently used at present and has been largely supplanted by the sustained released preparations. These are dosed at 6- to 12-hour intervals. Typical procainamide doses range from 2 to 6 gm/day in divided doses; however, doses as high as 12 gm/day can be tolerated by some patients.[121]

Administration of procainamide should be monitored by observation of the electrocardiogram for changes in the QRS- and JT-interval durations. Guidelines similar to those used for quinidine are appropriate while administering procainamide.

Monitoring plasma concentrations of procainamide may be very helpful. Generally, plasma concentrations between 4 and 10 μg/ml are desirable; however, in some patients, levels as high as 20 μg/ml are necessary and can be tolerated. Monitoring of plasma concentrations also allows identifications of unusual patients in whom marked accumulation of NAPA has occurred. Since this major metabolite of procainamide is an active antiarrhythmic agent and may accumulate to very high levels in certain patients, careful monitoring is necessary. Procainamide dosing may, in fact, be limited by accumulation of NAPA in individual patients.[92]

Efficacy

Procainamide is indicated for the treatment of both supraventricular and ventricular arrhythmias. The indications for procainamide are similar to those for quinidine. Although the indications are identical and the electrophysiologic effects of procainamide and quinidine are quite similar, both agents do not necessarily have the same effect in an individual patient. Procainamide is preferred over quinidine when emergent therapy is necessary because it is more readily administered intravenously. On the other hand, quinidine sometimes is preferred for supraventricular arrhythmias because of its presumed greater efficacy in such arrhythmias.

In early uncontrolled clinical trials, procainamide was reported to be effective for suppression of ventricular premature complexes in 90% of patients and for prevention of ventricular tachycardia in over 80% of patients.[173] Recently, more conservative estimates of its efficacy have been provided. Using Holter monitoring techniques, procainamide has been shown to be effective in suppression of ventricular premature complexes in 60% to 75% of patients.[115, 404] These estimates are also valid for the newer sustained released preparations.[115]