

A Primer and Update of Basic Cardiac Electrophysiology and Antiarrhythmic Agents

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Learning Objectives

After completing this continuing education program, the pharmacist will be able to:

1. Understand basic cardiac electrophysiology.
2. Understand the importance of major ions involved in cardiac electrophysiology.
3. Understand resting membrane potential, action potential, and refractory periods.
4. Explain major mechanisms of action of different antiarrhythmic agents.
5. Identify different classes of antiarrhythmic agents.
6. List major points about each antiarrhythmic agent discussed.

Abstract: Developing an adequate comprehension of arrhythmias and antiarrhythmic agents (AAAs) requires a basic knowledge of cardiac electrophysiology. Most clinicians find the understanding of arrhythmia and AAAs difficult. There are approximately 60 medications that directly affect cardiac electrophysiology. Additionally, there are several other non-cardiac medications that may affect the cardiac rhythm indirectly. The goal of this article is to present an understandable discussion of basic cardiac electrophysiology and a review of selected AAAs.



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INTRODUCTION

Cardiac electrophysiology is defined as the study of mechanisms, functions, and performance of electrical activities of the heart. Impulse initiation and conduction, resting membrane potential, action potential, and refractory periods are among major points to understand about cardiac electrophysiology.

RESTING MEMBRANE POTENTIAL

In resting cardiac cells the intracellular compartment is electrically negative compared with the extracellular compartment. This resting membrane potential (RMP) is normally maintained at -70 to -90 millivolts (mV) and is mainly supported by sodium (Na^+) and potassium (K^+) ions. Cardiac cells maintain a high intracellular to extracellular K^+ concentration and a low intracellular to extracellular Na^+ concentration. Additionally, at rest, a cardiac cell is permeable to K^+ ions and relatively impermeable to Na^+ , calcium, and chloride. Subsequent to K^+ ions passively diffusing out of the cell (efflux of K^+) and the inability of Na^+ to enter the cell (lack of influx of Na^+), a negative RMP of -70 to -90 mV is produced.

ACTION POTENTIAL

Usually, an electrical stimulus originated in adjacent cells causes depolarization and generation of an action potential (AP) in adjoining cells. In order for a cell to depolarize it must reach a threshold potential (approximately -60 to -70 mV for Purkinje fibers and -35 to -50 mV for nodal tissue) at which Na^+ influx increases and K^+ efflux decreases. The 5 phases of a ventricular AP include:

- Phase 0: upstroke with rapid Na^+ influx,
- Phase 1: rapid repolarization with rapid influx of chloride ion and an efflux of K^+ ,
- Phase 2: plateau that represents an influx of calcium ion concurrently with chloride ion,
- Phase 3: final repolarization with efflux of K^+ from the cell and decreased influx of calcium ion, and
- Phase 4: depolarization of the cells.

NORMAL IMPULSE INITIATION AND CONDUCTION OF THE HEART

A specialized system of tissues exists in the heart. This system is responsible for the initiation and conduction of electrical activity from pacemaker cells to the atria and ventricles. Normal electrical activity of the heart originates from the sinoatrial (SA) node. This electrical impulse then travels through a specialized conducting system in the atria, atrioventricular (AV) node, and finally into the ventricles.¹

When the cell is stimulated, the polarity of the cell is reversed. The inside of the cell becomes more positive relative to the outside of the cell. This process, known as depolarization, reflects the electrical current flow to all cells along the conduction pathways. Repolarization is when cells return to their original resting state.

The SA node, located in the junction of the superior vena cava and right atrium, is made up of a group of cells that possess spontaneous depolarization ability. Normal electrical activity of the heart should start at the SA node, which has the fastest intrinsic firing rate. Normally, the SA node firing rate determines the heart rate. In addition to the SA node, other areas of the heart,

like AV node and His-Purkinje system, also have pacemaking ability. If the SA node fails to maintain its pacemaking activity, the other mechanisms can allow a continuous cardiac electrical activity. The impulse initiated at the SA node propagates through the atria, which results in atrial contraction. Appearance of a “P” wave on an electrocardiogram (EKG) indicates the depolarization of the atria.¹

The number of SA nodal impulses reaching the ventricles is controlled by the AV node. The AV nodal and His-bundle conduction time represents the “P-R” interval on an EKG. The Bundle of His first divides into right and left branches and then divides into smaller branches called Purkinje fibers. The conduction through the branches and Purkinje fibers result in contraction of the ventricles and production of the “QRS” complex on an EKG. Ventricular repolarization, re-attainment of resting membrane potential, is represented with a “T” wave on EKG.¹

REFRACTORY PERIODS

There are 3 refractory periods during which a second AP cannot be normally produced:

- Absolute refractory period during which a stimulus can produce no depolarization,
- Effective refractory period (ERP) during which transient depolarization may occur but no AP may be propagated, and
- Relative refractory period during which stronger than normal stimuli may propagate AP.

MECHANISM OF ACTIONS OF ANTIARRHYTHMIC AGENTS

Antiarrhythmic agents (AAAs) may affect arrhythmia through one or more of the following mechanisms. They may affect:

- The action potential duration (APD),
- ERP/APD ratio,
- Threshold potential,
- Phase 0 (upstroke or V_{max}),
- Ca^{++} , K^+ , and Na^+ channels,
- Membrane permeability,
- Reentry,
- Sympathetic activity,
- SA and/or AV nodes conduction, and
- Other mechanisms.

CLASSIFICATION OF ANTIARRHYTHMIC AGENTS

The classification of AAAs is based on their effects on certain ion channels and receptors in the heart.² Although several attempts have been made to improve or revise the classification system developed by Vaughan Williams³ and subsequent modification by Harrison⁴, this system remains the clearest method of categorizing AAAs. Vaughan Williams originally categorized these agents into 4 different groups: class I, II, III, and IV. Class I agents were subclassified into classes IA, IB, and IC.

Agents like digoxin, adenosine, and magnesium are also used for the treatment of certain arrhythmias but are not officially assigned to the above classes. The following table describes the classes and the agents in each class.⁵

- Class IA: quinidine, procainamide HCl, disopyramide
- Class IB: lidocaine, mexilitine HCl, tocainide, phenytoin
- Class IC: flecainide acetate, propafenone HCl, moricizine
- Class II: beta-adrenergic blocking agents
- Class III: sotalol HCl, amiodarone, bretylium, ibutilide fumarate, dofetilide
- Class IV: calcium channel blocking agents

and also

- digoxin
- adenosine
- magnesium

- Class I AAAs primarily block the rapid influx of sodium current and slow the rate of phase 0.
- Class II agents, beta-adrenergic blocking agents, slow AV nodal conduction.
- Class III AAAs block the efflux of potassium current and increase refractoriness and slope of phase 3.
- Class IV agents, calcium channel blockers, block the slow inward calcium current.

It should be mentioned that some AAAs have more than one action and some might have primary and secondary effects. For example, agents like quinidine, sotalol, and amiodarone, among others, may possess actions consistent with different classifications.

It is also important to know that all AAAs have a potential to cause proarrhythmia. Proarrhythmia is a situation in which there exists the possibility of developing a new form of drug-induced arrhythmia or aggravation of existing arrhythmias. In some cases, proarrhythmia may be significant (ventricular tachycardia, ventricular fibrillation, or torsades de pointes), faster, longer, or with more frequent forms of existing arrhythmias. Patients with proarrhythmia may be totally asymptomatic, but on the other hand, some patients may suddenly die of proarrhythmia.

Some AAAs with their therapeutic uses and some important points to remember about each agent will be discussed.

Class II and IV agents, beta-blockers, and calcium channel blockers will only be briefly discussed.

CLASS IA AGENTS

These agents are often used to treat supraventricular and ventricular arrhythmias. The term “supraventricular arrhythmia” is applied to rhythms originating from centers proximal to the ventricles, and occurs mainly in the atrium, AV junction, and AV node. “Ventricular arrhythmias,” on the other hand, arise in the ventricles.

Quinidine, procainamide, and disopyramide belong to class IA category.

Quinidine

Quinidine is commonly used for the treatment of both supraventricular and ventricular arrhythmia. There are several important points to remember when prescribing or recommending quinidine for the treatment of arrhythmia:

- In treatment of patients with atrial fibrillation or flutter, quinidine, through several proposed mechanisms including significant atropine-like effect, peripheral alpha-adrenergic blockade and consequent reflex, or vagolytic effect, may allow more impulses to be conducted through the AV node. This can result in an increase in ventricular rate in response to the atrial rate. Therefore, AV nodal blockade must be established before the start of treatment with quinidine.
- Quinidine has a high incidence of gastrointestinal (GI) problems. Before termination of quinidine therapy because of GI side effects, clinicians should seek solutions to counteract these prevalent GI problems. Some suggested potential solutions are 1) allowing passage of time from the start of quinidine treatment, 2) treating the GI side effects with an aluminum-containing antacid, and 3) switching to a different formulation or salt form.
- Quinidine is available as gluconate (62% base) and polygalacturonate (60% base) salts as well as sustained release (SR) sulfate product. The SR product can be administered every 8 to 12 hours, while the conventional sulfate (83% base) salt can be administered every 6 to 8 hours.
- Because of other potential side effects of quinidine, complete blood count, liver and renal function, and Q-T interval need to be monitored periodically.
- Quinidine is approximately 80% to 90% protein bound, and has little bioavailability variations with route of administration. It is metabolized in the liver, and its half-life may increase in cirrhosis (from 6 to 8 hours to 8 to 10 hours).
- Quinidine has a potential to interact with several agents including digoxin and warfarin. In some instances, the dose of digoxin may need to be reduced by 50%. Some suggested mechanisms of interaction between quinidine and other agents include: 1) an increase in renal tubular reabsorption, 2) stimulation or inhibition of metabolizing enzymes, 3)

depression of vitamin K-dependent clotting factors, 4) change in volume of distribution, 5) potentiation of muscle relaxation, and 6) additive effects with other AAAs and antihypertensives.

Procainamide

Procainamide is commonly used to treat both supraventricular and ventricular arrhythmias. Additionally, wide complex tachyarrhythmias with an unknown cause or origin can be treated with procainamide. There are several important points to remember when prescribing or recommending procainamide for the treatment of arrhythmia:

- *N*-acetyl-procainamide (NAPA) is an active metabolite of procainamide that might exert some antiarrhythmic activity. When monitoring serum drug levels of procainamide, NAPA concentration and its activity should also be considered. The therapeutic range for procainamide is approximately 4 to 10 mcg/ml, and the range for NAPA is approximately 15 to 25 mcg/ml. Time to measure trough concentration of procainamide and NAPA is just before the next oral dose, or approximately 12 hours after the start of an intravenous (IV) infusion of procainamide. In evaluating therapeutic drug concentrations, it should be considered that NAPA has a longer half-life than procainamide.
- Procainamide does not appear to distribute into fat tissues significantly. Ideal body weight, in place of total body weight, should be used for procainamide, when the dosing is based on patient's weight.
- When administered IV, patients should be monitored for Q-T prolongation, hypotension, and resolution of arrhythmia. As the Q-T interval approaches 25% of the baseline, extreme caution should be used when considering further dose increases. A 50% prolongation of Q-T interval may signify the need for reducing the dose or abandoning therapy.
- Systemic lupus erythematosus (SLE) is a concern with procainamide therapy. SLE is a disease of unknown etiology in which cells and tissues are damaged by pathogenic immune complexes and autoantibodies. Clinical manifestations of SLE include systemic, musculoskeletal, cutaneous, hematologic, neurologic, cardiopulmonary, renal, GI, or ocular effects. Several drugs may cause a syndrome resembling SLE, including procainamide, hydralazine, isoniazid, chlorpromazine, D-penicillamine, practolol, methyldopa, quinidine, interferon, hydantoin, ethosuximide, and oral contraceptives. This syndrome is usually rare with all mentioned drugs except procainamide, the most frequent culprit, and hydralazine. Procainamide induces antinuclear antibodies (ANA) in 50% to 70% of individuals within a few months. Most common symptoms associated with SLE are systemic complaints (fatigue, malaise, fever, anorexia, nausea, weight loss) and arthralgias.
- Procainamide is commercially available in immediate-release and long-acting formulations, including the newly released, twice daily dosed formulation. It has been reported that the remnant of the total dosage form of some long-acting formulations, called "ghost tablet," has appeared as an intact wax matrix in the feces.

- Clinicians should remember that renal function and cardiac output may affect the pharmacokinetics of procainamide. Procainamide's half-life for normal patients is approximately 3.5 hours, while in anephric patients is approximately 5 to 20 hours, with an average of approximately 10 hours. NAPA is much more dependent on renal function. NAPA's half-life for normal patients is approximately 4 to 15 hours, while in anephric patients can be as long as approximately 40 hours. It is best to avoid use of NAPA in patients with significant renal impairment. If it is used, procainamide, NAPA, and the patient's clinical status should be monitored closely. Metabolism of procainamide is equally hepatic and renal. The dose also needs to be adjusted in patients with hepatic dysfunction.

Disopyramide

Disopyramide can be used for treating both supraventricular and ventricular arrhythmias. The most common drug adverse effects of disopyramide include anticholinergic effects: urinary retention, blurred vision, dry mouth, and constipation. These anticholinergic side effects can occur in approximately 10% to 30% of patients. The reference therapeutic range for disopyramide is approximately 2 to 8 mcg/ml. The dose needs to be adjusted based on the patient's renal function. Unlike procainamide and quinidine, this agent is only available in oral form and is not prescribed very often.

CLASS IB AGENTS

Class IB AAAs are often used to treat ventricular arrhythmia. Lidocaine, mexilitine, tocainide, and phenytoin belong to class IB.

Lidocaine

Lidocaine is a class IB AAA. It is used to treat ventricular tachycardia and ventricular fibrillation. At therapeutic concentration, lidocaine has little or no effect on the SA node and on conduction through the atria. There are several important points to remember when prescribing or recommending lidocaine for the treatment of arrhythmia:

- Lidocaine has poor oral bioavailability because of extensive first-pass metabolism, but oral doses large enough to produce therapeutic serum levels can result in central nervous system (CNS) and GI toxic effects.
- For treatment of arrhythmia, lidocaine is usually administered intravenously (IV). When the IV route is not feasible, other routes of administration, intramuscular (IM) and endotracheal (ET), can also be used. Lidocaine is well absorbed over 15 to 30 minutes when it is administered IM. It is also well absorbed by the ET route in approximately 1 minute. Lidocaine has also been administered intranasally. About 50% of the lidocaine dose can reach the systemic circulation when given intranasally.
- Lidocaine is approximately 70% protein bound at therapeutic serum levels of 2 to 5 mg/L, but it is approximately 60% protein bound at 6 to 10 mg/L. This excess unbound drug can cross into the CNS and cause toxic reactions.
- Lidocaine is metabolized in the liver to 2 metabolites, both of which may exhibit antiarrhythmic activity.

- Lidocaine clearance decreases with continuous maintenance infusions. Potential for toxicity should be considered for every patient on lidocaine infusions longer than 24 hours. In these patients, the half-life can double or triple with corresponding increases in the serum concentration. Serum concentration should be monitored in all patients who receive lidocaine for longer than 24 hours.
- Half-life of lidocaine may increase in patients who are elderly or with hepatic failure, renal failure, large myocardial infarction, congestive heart failure (CHF), or shock. These patients are at greatest risk of manifesting toxicity because of their diminished capacity for metabolizing lidocaine. Although normal half-life of lidocaine is approximately 2 hours, the half-life can increase up to 72 hours in patients with CHF and up to 7 hours in patients with liver failure. These patients should be monitored closely, lidocaine serum concentration should be measured, and the dose needs to be adjusted in order to avoid lidocaine toxicity.
- Lidocaine toxicity may include agitation, tinnitus, visual disturbances, confusion, paresthesias, or seizures. In case of toxicity, lidocaine should be discontinued and supportive treatment should be provided. Seizures may be treated with benzodiazepines or barbiturates.
- Because of the half-life of lidocaine (approximately 2 hours for patients with normal cardiac output), it may be discontinued without a downward dose titration.
- Minimum effective serum lidocaine concentration is approximately 1 to 2 mg/L, and the therapeutic range for lidocaine is approximately 2 to 5 mg/L.

Mexiletine

Mexiletine is an analogue of lidocaine but it is only available for oral use. Although mexiletine has no therapeutic activity in the treatment of atrial arrhythmias, it can be effective in suppressing ventricular ectopy. Ectopy denotes a heartbeat that has its origin in some abnormal focus or develops from a focus other than the SA node. Patients on mexiletine should be monitored for GI and CNS side effects like tremor and confusion. These side effects are often the dose-limiting factors. The GI side effects may be minimized by taking the drug with food. Therapeutic reference range for mexiletine is approximately 0.4 to 2 mcg/ml. A lower dose should be administered in patients with CHF or hepatic failure.

Tocainide

Tocainide is used for suppression and prevention of symptomatic life-threatening ventricular arrhythmias. It is only available in oral form. A lower dose should be used in patients with renal or hepatic impairment. Therapeutic reference range for tocainide is approximately 5 to 12 mcg/ml.

CLASS IC ANTIARRHYTHMIC AGENTS

Class IC AAAs can be used for the treatment of supraventricular and ventricular arrhythmias. Flecainide and propafenone belong to class I-C AAAs.

Flecainide

Flecainide is used for treatment of supraventricular and ventricular arrhythmias. It is only available for oral use. GI and CNS are the most common side effects associated with flecainide. A lower dose should be used in patients with renal or hepatic impairment. Therapeutic reference range for flecainide is approximately 0.2 to 1 mcg/ml. It can interact with a number of other agents including digoxin, so patients should be monitored for possible drug-drug interactions.

Propafenone

Propafenone is used for treatment of supraventricular and ventricular arrhythmias. In addition to class IC activity, propafenone has some class II and IV effects. It is only available for oral use. A lower dose should be used in patients with hepatic impairment. It can interact with a number of other agents including digoxin, so patients should be monitored for possible drug-drug interactions. The serum concentration of digoxin might increase by approximately 80% and the anticoagulant effect of warfarin might increase by approximately 40%. Dizziness, nausea, and a metallic taste are among the most common side effects associated with propafenone. In treatment of atrial fibrillation or atrial flutter, propafenone, similar to quinidine, can enhance the ventricular rate if AV nodal blockade is not established.

CLASS II ANTIARRHYTHMIC AGENTS

Beta-adrenergic blocking agents are classified as class II AAAs. These agents are often used for the control of ventricular rate in patients with chronic atrial fibrillation. Beta-adrenergic blocking agents vary based on their effects on different receptors (beta₁, beta₂, and alpha), lipid solubility, half-life, formulation, route of administration, approved indications, and possession of intrinsic sympathomimetic and membrane stabilizing activities.

CLASS III ANTIARRHYTHMIC AGENTS

Class III AAAs are used in the treatment of supraventricular and ventricular arrhythmias (amiodarone and sotalol), supraventricular arrhythmias (ibutilide and dofetilide), and ventricular arrhythmias (bretylum).

Amiodarone

Amiodarone was originally developed in Belgium as an anti-anginal agent. It is usually efficacious in approximately 75% of patients in whom other AAAs were ineffective. There are several important points to remember when prescribing or recommending amiodarone for the treatment of arrhythmia:

- Amiodarone is notorious for having a number of potentially serious side effects. A great majority of patients on long-term amiodarone will experience at least one side effect. Adverse reactions may affect cardiovascular and pulmonary systems, thyroid, GI, liver, eye, and skin. Amiodarone can also cause gynecomastia, sterile epididymitis, and epidermal necrolysis. Some of amiodarone side effects are dose-related and some are reversible upon discontinuation. The maintenance doses should be kept at the lowest possible levels in order to minimize adverse events. Because of amiodarone's serious side effects, clinicians should perform a baseline assessment of patients before initiation. This may include eye, thyroid, liver, pulmonary, GI, and dermatologic assessments.

- Although the onset of action for oral amiodarone is from approximately 2 to 3 days to 1 to 3 weeks, the maximum antiarrhythmic activity may not be observed for 1 to 5 months.
- Different loading regimens have been suggested for amiodarone. Some clinicians start the oral treatment with 800 to 1600 mg/day for 1 to 3 weeks, 600 to 800 mg/day for 1 to 3 weeks, and then begin a maintenance dose of 100 to 400 mg/day, thereafter. Another loading regimen could be 2000 mg on day 1, 1400 mg/day for 3 days, 1000 mg/day for 7 days, 800 mg/day for another 1 to 2 weeks, and the desired maintenance is given, thereafter. The selected loading regimen and maintenance doses usually depend on the type of arrhythmia (supraventricular vs. ventricular). The loading dose is usually divided into 3 to 4 increments, and should be administered with food in order to minimize the GI problems associated with amiodarone.
- The distribution half-life of amiodarone ranges from 2 to 10 days, and its elimination half-life is 53 days on average. Amiodarone has a very large volume of distribution, an average of 66 L/kg, indicating vast tissue accumulation. Amiodarone is 96% protein bound, mainly to albumin. It is extensively metabolized in the liver and intestinal mucosa to at least one major metabolite and is excreted by the feces via the bile.
- Amiodarone can cause serious drug-drug interactions. Doses of drugs like digoxin, warfarin, and flecainide might have to be reduced by half to avoid toxicities. The doses for procainamide, quinidine, calcium channel blockers, and beta-blockers should be reduced from one-third to one-half. Phenytoin serum concentration may increase by 3 to 4 fold. Clinicians should remember that the potential for drug-drug interactions can continue months after the drug is discontinued. Amiodarone may interfere with clearance, bioavailability, thyroid function, and renal elimination. Amiodarone can also cause displacement from tissue stores, inhibition of vitamin K—dependent clotting factors, and competition for protein binding.
- Intravenous amiodarone, on the other hand, can achieve some antiarrhythmic activity within 2 hours in some patients. It should be remembered that IV amiodarone can cause serious infusion rate-related hypotension, and should be reserved for patients with life-threatening arrhythmias. The dose of IV amiodarone for the first 24 hours is 150 mg over the first 10 minutes, 360 mg over the next 6 hours, and 540 mg should be administered over the next 18 hours. After the first 24 hours, the infusion dose is 0.5 mg/min. Bolus doses of 150 mg can also be administered over 10 minutes for breakthrough arrhythmia. A central line should be used if the amiodarone concentration is above 2 mg/ml, and infusions lasting longer than 2 hours must be prepared in glass containers.

Sotalol

Sotalol is a non-cardioselective beta-blocker with both beta₁ and beta₂ effects. It possesses class II and class III antiarrhythmic activities, and it is only available in oral formulation. Sotalol has been used in treatment of ventricular and supraventricular arrhythmias. Sotalol was recently approved for the maintenance of normal sinus rhythm in patients with symptomatic atrial fibrillation or atrial flutter who are currently in sinus rhythm. Because sotalol can cause life-

threatening arrhythmias, it should be reserved for patients in whom atrial fibrillation or atrial flutter is highly symptomatic.

The dose of sotalol should be adjusted based on the patient's renal function. The doses should be administered at longer intervals for patients with creatinine clearance of less than 60 ml/min. Patients treated with sotalol should be monitored for potential drug-drug interactions including its interaction with calcium channel blocking agents.

Ibutilide

Ibutilide, available only in IV formulation, is indicated for acute termination of atrial fibrillation or atrial flutter of recent onset. Thirty to fifty percent of patients with atrial fibrillation and 50% to 70% of patients with atrial flutter of less than 30 days' duration may convert to sinus rhythm with ibutilide. The dose of ibutilide for patients who weigh less than 60 kg is 0.01 mg/kg over 10 minutes and for those who weigh more than 60 kg is 1 mg over 10 minutes. This dose may be repeated once more if needed.

Ibutilide may be administered undiluted or diluted. During administration of ibutilide, EKG should be continuously monitored for Q-T prolongation and effectiveness. Infusion of ibutilide should be stopped when atrial arrhythmia is terminated, Q-T prolongation is noted, or ventricular arrhythmia is observed.

Patients should also be monitored for several serious drug-drug interactions, especially with other AAAs, phenothiazines, tricyclic antidepressants, and non-sedating antihistamines. These drugs have a potential of Q-T interval prolongation and can increase the risk of torsades de pointes associated with the use of ibutilide. Risk of torsades de pointes is a major concern with use of ibutilide. This drug should be administered where cardiac resuscitation equipment and skilled personnel are present.

Bretylum

Bretylum can be useful in treatment of ventricular arrhythmia. It is not available in oral form. Due to the initial norepinephrine release after the administration of bretylum, clinicians should be aware that the antiarrhythmic activity of bretylum might be delayed for approximately 6 to 20 minutes.

Patients treated with bretylum should be monitored for hypotension and vomiting. The dose of bretylum should be adjusted based on the patient's renal function.

Dofetilide

Dofetilide has been recently approved for the maintenance of normal sinus rhythm in patients with atrial fibrillation or flutter of greater than 1 week's duration, who have been converted to normal sinus rhythm. It is also indicated for the conversion of atrial fibrillation or flutter to normal sinus rhythm.

It inhibits potassium current, and has no effect on sodium channels.

Q-T interval must be determined prior to administration of the first dose of dofetilide. Its usual oral adult dosage is initially 500 mcg twice daily. The initial dosage must be adjusted in patients with an estimated creatinine clearance of less than 60 mL/min. The initial dose is 250 mcg twice daily for a patient with a creatinine clearance of 40 to 60 mL/min and the dose is 125 mcg twice daily for a patient with a creatinine clearance of 20 to 39 mL/min. In patients with a creatinine clearance of less than 20 mL/min, the use of dofetilide is contraindicated. Based on the manufacturer's recommendation, the modification of dosage in response to initial dose is as follows:

Corrected Q-T (QT_c) interval should be measured 2 to 3 hours after the initial dose. If the QT_c interval is greater than 15% of baseline or if the QT_c interval is greater than 500 msec (550 msec in patients with ventricular conduction abnormalities), then the dofetilide dose should be adjusted.

- If the starting dose was 500 mcg twice daily, then the dose needs to be adjusted to 250 mcg twice daily.
- If the starting dose was 250 mcg twice daily, then the dose needs to be adjusted to 125 mcg twice daily.
- If the starting dose was 125 mcg twice daily, then the dose needs to be adjusted to 125 mcg once daily. The QT_c interval must be determined 2 to 3 hours after each subsequent dose of dofetilide for in-hospital doses.
- If the measured QT_c interval is greater than 500 msec (550 msec in patients with ventricular conduction abnormalities), then dofetilide should be discontinued.

No dosage adjustment is recommended in patients with hepatic impairment and the elderly.

Dofetilide is only available to institutions and practitioners who have been trained in the use of this agent. Dofetilide is not currently available in pharmacies, and it is distributed only through a single-source, mail-order pharmacy. The initiation of therapy with dofetilide and, if necessary, re-initiation, need to be accomplished in an in-patient setting. It is supplied as 125, 250, and 500 mcg capsules.

Because dofetilide can cause life-threatening arrhythmias, it should be reserved for patients in whom atrial fibrillation or atrial flutter is highly symptomatic.

CLASS III ANTIARRHYTHMIC AGENTS AND TREATMENT OF HEART FAILURE

At this point, it is important to add that arrhythmia is common in patients with heart failure, and can lead to several deleterious effects. The maintenance of a normal sinus rhythm is an important factor in determining clinical course and symptoms of patients with severe heart failure. Unfortunately, several AAAs have been shown to increase mortality in heart failure patients. Amiodarone and dofetilide in class III AAAs have shown some favorable outcomes in treatment of arrhythmia for patients with heart failure.⁶⁻⁸ Other AAAs that do not belong to class

III (i.e., digoxin and some beta-adrenergic blocking agents) have also been used successfully in treatment of heart failure patients.

CLASS IV ANTIARRHYTHMIC AGENTS

Calcium channel blocking agents, specifically phenylalkylamine (verapamil) and benzothiazepine (diltiazem), exert their effect on the AV node by decreasing automaticity and prolonging nodal conduction. These agents alone or in combination with other AAAs, like digoxin, have shown to slow the ventricular response in atrial fibrillation and atrial flutter.

DIGOXIN

Digoxin modifies cardiac mechanical and electrical activities. The overall effects of digoxin result in a composite of changes in heart rate and force of ventricular contraction. Digoxin is one of the most commonly prescribed drugs. It is used in the management of patients with heart failure, atrial fibrillation, atrial flutter, and paroxysmal atrial tachycardia.

Digoxin's narrow therapeutic index makes it a major cause of drug toxicity. Cardiac and non-cardiac toxic effects of digoxin are common, and can be serious and frequent. It has been estimated that up to 35% of digitalized patients may experience digitalis-related toxicity. Two of the medications used in the management of digoxin toxicity include digoxin-specific antibody fragments (Fab) in life-threatening intoxications, when fast reversal of intoxication is crucial; and oral-activated charcoal, with a slow onset of action in non—life-threatening toxicities. Because of several disadvantages of Fab, its use should be reserved for specific patients. Some of Fab's limitations are:⁹

- Reported cases of hypokalemia,
- Exacerbation of congestive heart failure because of a rapid loss of inotropic support from digoxin,
- Hypotensive episodes,
- Inability to measure and interpret serum digoxin concentrations for a long time (up to > 1 week) after administration of Fab due to measurement of “total” serum digoxin concentration by most conventional assay techniques,
- Unavailability of an oral form,
- Inability to re-administer the Fab in future toxicities owing to lack of effectiveness or a higher possibility of anaphylaxis,
- Serum sickness or febrile reactions,
- Inability of some clinicians to accurately calculate the required amount of Fab,
- Potential for immediate hypersensitivity to the heterologous Fab fragments (some studies suggest skin testing), and

- An extremely high acquisition cost of the drug (in thousands of dollars per treatment).

There are several important points to remember when prescribing or recommending digoxin for the treatment of arrhythmia:

- Bioavailability of digoxin varies with the formulation: 70% from tablet, 80% from IM, 85% from elixir, and 95% from capsule. Erythromycin and tetracycline may increase digoxin bioavailability (by approximately 43% to 116%) through prevention of digoxin metabolism by bacteria located within the GI tract.
- Digoxin shows little affinity for distribution into fat, so ideal body weight should be used for dosing. Digoxin has a high target-organ uptake; reported myocardial/serum digoxin concentration ratios are approximately 30:1 in adults and 125:1 to 150:1 in children.
- Elimination of digoxin is primarily by the renal route, where 60% to 80% of bioavailable digoxin is excreted unchanged by the kidneys. Renal diseases may substantially alter the elimination half-life of digoxin. Half-life of digoxin in patients with normal renal function is approximately 1.6 days, whereas in anephric patients it ranges from 3.5 to 4.5 days.
- Therapeutic drug monitoring may reduce the variability in plasma drug concentrations. A relationship may exist between the plasma drug concentration and the drug pharmacologic effect of digoxin.
- Clinicians should monitor the patients for all possible drug-drug interactions with digoxin. The digoxin dose needs to be adjusted based on renal function and diagnosis of the patient (CHF vs. control of rapid ventricular response). The therapeutic range for digoxin is approximately 0.5 to 2.0 ng/mL. A higher level may be needed for control of rapid ventricular response.
- Serum digoxin concentration should be measured at least 4 hours after IV, 12 hours after IM, and at least 6 to 8 hours after oral digoxin administration (optimally 12 to 24 hours after a dose).
- Some signs and symptoms of digoxin toxicities may include GI, CNS, and cardiovascular manifestations. Serum K^+ levels should be monitored closely.

ADENOSINE

Adenosine is an IV AAA with an extremely short half-life of fewer than 10 seconds. It is used in the treatment of paroxysmal supraventricular tachycardia including that associated with accessory bypass tracts. Adenosine is not the drug of choice in the treatment of atrial fibrillation, atrial flutter, or ventricular tachycardia.

Owing to its pharmacologic action, clinicians should expect to observe a short period of heart block, sinus pause, or asystole after administration of adenosine. Adenosine can cause flushing, shortness of breath, and apprehension. Drugs like methylxanthines can antagonize the effects of adenosine, and dipyridamole and carbamazepine may potentiate the effects of adenosine.

The initial dose of adenosine is a rapid IV bolus of 6 mg. If that is ineffective within 1 to 2 minutes, an additional 12 mg may be given. An additional 12 mg may also be administered up to a total dose of 30 mg. Adenosine should be administered rapidly at an injection site closest to the patient's heart. Each bolus dose should be followed with a normal saline flush. Both adenosine and a normal saline flush should be prepared in advance to avoid wasting time, in light of adenosine's short half-life.

MAGNESIUM

Magnesium sulfate has several therapeutic uses. As an AAA, it is often used in the management of patients with torsades de pointes. In this setting, 1 to 2 grams of magnesium sulfate is administered as a slow IV push.

OTHERS

Other agents including azimilide, dronedarone, tedisamil, and trecetilide are under study to determine their usefulness in patients with cardiac arrhythmia.

CONCLUSIONS

Considering that there are approximately 60 medications that affect cardiac electrophysiology directly in addition to several other non-cardiac medications¹⁰ that affect cardiac rhythm indirectly, every clinician should have an understanding of basic electrophysiology and AAAs.

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