Drug Therapy in Adult Congenital Heart Disease

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KEYWORDS

• Drug therapy • Anticoagulation • Congenital heart disease • Arrhythmia

KEY POINTS

- Class I antiarrhythmic drugs (sodium channel blockers) should be used with caution in patients having ventricular scar, decreased ejection fraction, significant mitral regurgitation and significant PR prolongation.
- Flecainide and Propafenone are the most potent and commonly used class I antiarrhythmics; there are several differences between these 2 medications that are important to remember for day to day use.
- Class III antiarrhythmic drugs (potassium channel blockers) have been used in the setting of ventricular scar. Most of these also have negative inotropic effects.
- Amiodarone is the most commonly used antiarrhythmic drug which has significant long-term side effects including lung, liver, thyroid and neurological abnormalities.
- Sotalol and dofetilide are the other commonly used class III antiarrhythmics; these can result in a dose-dependent QTc prolongation requiring close monitoring at the time of initiation. There are several differences between these 2 medications that are important to remember for practical use.

INTRODUCTION

With advances in cardiology, patients born with moderate and even complex congenital heart disease are living well into adulthood.[1] Structural abnormalities predispose them to not only pump-related issues but also complex atrial as well as ventricular arrhythmias leading to significant morbidity and mortality.[2] These arrhythmias are not always amenable to ablation and many of these patients require antiarrhythmic drug therapy, sometimes in conjunction with ablative approaches. In addition, the risk of systemic thromboembolism is high in patients with moderate and severe forms of congenital heart disease who develop atrial arrhythmias.[3] Anticoagulation with warfarin and now the non—vitamin K antagonist oral anticoagulants (NOACs) is often required in these patients.

Although the principles of use of antiarrhythmic therapy in patients with adult congenital heart disease are similar to those in the general population, important differences exist:

1. The heart is structurally abnormal and there is presence of atrial as well as ventricular scar in many of these patients, which alters the pharmacodynamics of antiarrhythmic drugs.
2. Renal and hepatic function may be abnormal in these patients and may alter the pharmacokinetics of these medications.
3. Clinical data on the use of antiarrhythmic medications in this patient population are scant, and hence most recommendations are based on opinion.

This article summarizes the use of antiarrhythmic and anticoagulant drugs in patients with adult congenital heart disease and highlights features of these medications that are important for clinicians to remember when dealing with this patient population.

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ANTIARRHYTHMIC DRUGS

The pharmacologic effects of each antiarrhythmic drug are highly variable. The widely used Vaughan-Williams[4] classification scheme does not adequately describe the antiarrhythmic effect of each of its classes and there is significant overlap. The Sicilian gambit classification[5] scheme, although more specific, is tedious and less practical to use on a daily basis.

Based on the more commonly used Vaugh-Williams[4] classification scheme, antiarrhythmic drugs are classified into 4 groups:

1. Class I agents: predominantly sodium channel blockers
2. Class II agents: β-blockers
3. Class III agents: predominantly potassium channel blockers
4. Class IV agents: calcium channel blockers

In addition to these, there are several medications, such as ranolazine, adenosine, digoxin, and magnesium, that have not found a place in this classification scheme.

A general description of antiarrhythmic drug is provided next that is applicable to all patients; recommendations are included (if available) for use in congenital heart disease populations.

CLASS I ANTIARRHYTHMIC AGENTS

The class 1 antiarrhythmic agents are predominantly sodium channel blockers and include 3 subclasses. These medications can be pro-arrhythmic in the presence of myocardial scar and should be avoided in patients with congenital heart disease and significant ventricular scarring. Additionally, most of the medications in the class have significant negative inotropic effects and should be avoided in patients with congestive heart failure. These medications can also worsen forward flow in patients with significant mitral regurgitation. Many patients with congenital heart disease can have a first degree AV block; Class 1 agents should generally be avoided if the PR interval is >250 to 300 ms to avoid AV dys-synchrony related side-effects. Class IA, 1B and 1C medications have intermediate, fast and slow kinetics, respectively. The slow kinetics of the class IC agents results in slow unbinding of these medications from the ion channels making these the most potent sodium channel blockers. Details regarding these medications are outlined in **Table 1**.

Class 1 Agents in Patients with Congenital Heart Disease

There are not many studies that have evaluated the safety and efficacy of class I antiarrhythmic agents in patients with adult congenital heart disease. There is a fear of proarrhythmic effects of these medications given the underlying scar. In a study in young patients who were administered class IC agents, proarrhythmic events were observed in close to 8% of patients, especially in those with underlying structural heart disease.[6] Class I agents were also associated with the increased risk of ventricular arrhythmias when used in patients with tetralogy of Fallot.[7] Although class I antiarrhythmics are usually not recommended in patients with so-called structural heart disease, they are used in patients with congenital heart disease with caveats (discussed later).

A brief description of these medications follows.

Class 1A antiarrhythmics

Quinidine This was one of the first antiarrhythmic drugs used. It has excellent oral absorption, and is predominantly excreted through the liver. It has fast sodium channel blocking properties; however, it also blocks the potassium channels (prolonging QT interval) and has autonomic effects. Over time, the dangers associated with its use have been recognized and hence it is rarely used in contemporary practice. Its most serious adverse effect is a dose-independent increase in the corrected QT (QTc) interval leading to torsades de pointes.[8]

Quinidine can potentially be used in patients with ventricular arrhythmias and simple congenital heart disease (especially if they have an implantable cardioverter defibrillator [ICD] as backup), but its only practical contemporary use is in patients with Brugada syndrome.[9] By blocking the Ito channel, quinidine can reduce the transmyocardial electrical gradient during the repolarization, preventing phase II reentry in patients with Brugada syndrome.[10]

Procainamide Procainamide also has potassium channel blocking as well as autonomic effects in addition to sodium channel blocking properties. It has good oral absorption but it is also available in the intravenous form. It has a complex metabolism whereby it is metabolized in the liver to *N*-acetyl procainamide (NAPA), which is then excreted renally. NAPA has predominantly potassium channel blocking properties and can accumulate in renal dysfunction, leading to QTc prolongation/torsades de pointes.[11] In contrast, slow acetylators of procainamide[12] (which can be up to 50% of the population) or patients with hepatic dysfunction generate less NAPA and hence have less class III action. Similar to quinidine, procainamide also causes dose-independent QTc prolongation. It can cause ANA (anti-nuclear antibody) positivity in up to 80% of the patients; however, systemic lupus erythematosus develops in only 30% of these patients.[13]