Use of antiarrhythmic drugs in elderly patients

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Use of antiarrhythmic drugs in elderly patients

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Abstract

Human aging is a global issue with important implications for current and future incidence and prevalence of health conditions and disability. Cardiac arrhythmias, including atrial fibrillation, sudden cardiac death, and bradycardia requiring pacemaker placement, all increase exponentially after the age of 60. It is important to distinguish between the normal, physiological consequences of aging on cardiac electrophysiology and the abnormal, pathological alterations. The age-related cardiac changes include ventricular hypertrophy, senile amyloidosis, cardiac valvular degenerative changes and annular calcification, fibrous infiltration of the conduction system, and loss of normal pacemaker cells and these changes could have a profound effect on the development of arrhythmias. The age-related cardiac electrophysiological changes include up- and down-regulation of specific ion channel expression and intracellular Ca2+ overload which promote the development of cardiac arrhythmias. As ion channels are the substrates of antiarrhythmic drugs, it follows that the pharmacokinetics and pharmacodynamics of these drugs will also change with age. Aging alters the absorption, distribution, metabolism, and elimination of antiarrhythmic drugs, so liver and kidney function must be monitored to avoid potential adverse drug effects, and antiarrhythmic dosing may need to be adjusted for age. Elderly patients are also more susceptible to the side effects of many antiarrhythmics, including bradycardia, orthostatic hypotension, urinary retention, and falls. Moreover, the choice of antiarrhythmic drugs in the elderly patient is frequently complicated by the presence of co-morbid conditions and by polypharmacy, and the astute physician must pay careful attention to potential drug-drug interactions. Finally, it is important to remember that the use of antiarrhythmic drugs in elderly patients must be individualized and tailored to each patient’s physiology, disease processes, and medication regimen.

Keywords: aging; antiarrhythmic drugs; pharmacokinetics; pharmacodynamics; polypharmacy; cardiac electrophysiology; ion channels

1 Issues of global aging

Elderly people constitute a larger segment of the population today than at any other time in history. In 1900, only 4% of the population in the United States was 65 or older. In 2000, more than 40 million people were in that age group, representing nearly 13% of the population. By 2030, when the last wave of baby boomers reaches the age of 65, elderly people are expected to constitute over 20% of the U.S. population.[1]

Moreover, human aging is a global issue. Based on census and population projections from 1950 to 2050, there has been a worldwide transformation of the distribution of the population by age, from a population pyramid to a population dome (Figure 1). This trend applies to both male and females, in developing countries as well as in developed countries.[2] In fact, the large population in the developing world contributes significantly to the transformation in demographics. These trends in the global patterns of aging have important implications for the current and future incidence and prevalence of many health conditions. With the advance in overall age comes an increase in the incidence of cardiovascular diseases, including cardiac arrhythmias. Global aging has important implications for health care delivery, as age-related physiological changes are frequently overlooked when treatment options are considered and may result in unnecessary adverse outcomes. This review will focus on issues pertaining to the pharmacologic treatment of cardiac arrhythmias in the elderly population.

2 Aging and cardiac arrhythmias

The prevalence of cardiac diseases, including cardiac...
arrhythmias, increases with age. Increased frequencies of supraventricular and ventricular ectopies have been reported in elderly patients. Additionally, elderly patients have a heightened propensity to develop certain arrhythmias, including atrial fibrillation, sudden cardiac death, and bradyarrhythmias requiring pacemaker placement. Results
from the ATRIA (AnTicoagulation and Risk Factors in Atrial fibrillation) study showed that there is an exponential increase in the prevalence of atrial fibrillation after the age of 60 for both men and women, with over 10% of people older than 80 years of age affected.\[8\] Based on these results, it is projected that by 2050, the majority of patients with atrial fibrillation will be 80 years or older. Similarly, the incidence of sudden cardiac death in the general population shows an exponential increase after 55 years of age, peaking in the seventies and eighties. This affects both men and women, with women accounting for 43% of sudden cardiac death cases.\[9,10\] There is also a remarkable age-related increase in bradyarrhythmias, both in sinus nodal dysfunction and in atrioventricular (AV) blocks. The incidence of first time pacemaker implantation increases substantially after the age of 60, peaking in the seventies and leveling off in the eighties.\[11,12\]

## 4 Changes in cardiac ion channels with aging

The age-related electrocardiogram (ECG) and action potential changes are associated with changes in the properties and activities of specific ion channels (Table 1).\[23,24\] Among the inward currents, the voltage-gated sodium channel is unaltered with age,\[25\] but the L-type Ca\(^{2+}\) currents (\(I_{\text{CaL}}\)) are increased with delayed inactivation in the ventricles,\[26\] while becoming significantly reduced by more than 40% in the atria.\[27\] On the other hand, among the repolarizing currents in the ventricles, the transient outward \(K^+\) currents (\(I_{\text{to}}\)) and the ATP-sensitive \(K^+\) currents (\(I_{\text{KATP}}\)) are reduced.\[28\] These, together with the enhanced \(I_{\text{CaL}}\), result in lengthened action potential durations and prolonged QT intervals. Meanwhile, the strong inward rectifier \(K^+\) currents (\(I_{\text{Kr}}\)) are unchanged.\[29\]

### Table 1. Change in cardiac ionic currents with old age.

<table>
<thead>
<tr>
<th>Currents</th>
<th>Change in aging</th>
</tr>
</thead>
<tbody>
<tr>
<td>(I_{\text{Na}}) Atria: ↔, Sinus node: ↓</td>
<td></td>
</tr>
<tr>
<td>(I_{\text{CaL}}) Ventricles: ↑, delayed inactivation Atria: ↓ by 40%, Sinus node: ↓</td>
<td></td>
</tr>
<tr>
<td>(I_{\text{Ks}})</td>
<td>↓</td>
</tr>
<tr>
<td>(I_{\text{AHP}})</td>
<td>↓</td>
</tr>
<tr>
<td>(I_{\text{Kr}}) Atria: ↑</td>
<td></td>
</tr>
<tr>
<td>(I_{\text{K}})</td>
<td>↔</td>
</tr>
<tr>
<td>(I_{\text{Ko}})</td>
<td>↑</td>
</tr>
<tr>
<td>SERCA-2</td>
<td>↑</td>
</tr>
<tr>
<td>(C_{\text{x}}) Atria and ventricles: ↓</td>
<td></td>
</tr>
<tr>
<td>(HCN4) Sinus node: ↓-mRNA</td>
<td></td>
</tr>
<tr>
<td>APD Atria and ventricles: ↑</td>
<td></td>
</tr>
</tbody>
</table>

\(I_{\text{Na}}\): voltage-gated sodium currents; \(I_{\text{CaL}}\): L-type calcium currents; \(I_{\text{K}}\): transient outward potassium currents; \(I_{\text{AHP}}\): ATP-sensitive potassium currents; \(I_{\text{Kr}}\): ultra-rapid delayed rectifier potassium currents; \(I_{\text{Ko}}\): strong inward rectifier potassium currents; \(I_{\text{Ko}}\): sodium-calcium exchange currents; SERCA-2: sarcoplasmic reticulum calcium pump; \(C_{\text{x}}\) Atria and ventricles: ↓ |  |

Normal aging is associated with a reduced autonomic response to stress, including decreased baroreflex buffering and depressed heart rate variability.\[21\] There is an increase in the prevalence of orthostatic hypotension and supine hypertension with age; however, the presence of baroreceptor and autonomic failure is abnormal.\[22\] Because of these alterations, the cardiac electrophysiological changes that occur with age reduce the margin of functional reserve and render the aging heart more susceptible to the development of electrophysiological abnormalities. In addition, the age-related cardiac changes which include ventricular hypertrophy, senile amyloidosis, cardiac valvular degenerative changes and annular calcification, fibrous infiltration of the conduction system, and loss of natural pacemaker cells could also have profound direct and indirect effects on the development of arrhythmias.

### 3 Changes in cardiac electrophysiology with aging

Cardiac electrophysiological properties change with age, and it is essential to differentiate between normal, physiologic consequences of aging versus abnormal, pathological transformations. First, intrinsic heart rate decreases with age.\[13\] Heart rate response is blunted with advanced age, though excessive sinus pauses are not considered physiologic.\[14\] Second, the PR interval becomes prolonged with age. First degree AV block is common among elderly people, but second and third degree AV blocks are abnormal. These changes are associated with AH prolongation without alteration of the HV interval.\[15\] Third, conduction system changes in the form of right bundle branch block (RBBB) are more common in elderly patients and are not associated with cardiac morbidity or mortality, but the presence of left bundle branch block (LBBB) in older patients is frequently an indication of the presence of underlying cardiac disease\[4\] and is associated with adverse outcomes.\[16\] Fourth, atrial and ventricular ectopies are known to increase with age, but atrial fibrillation and ventricular tachycardia should not be considered normal.\[17,18\]

Fifth, age-related non-specific ST-T wave changes are common, but the presence of Q waves is seldom normal. Sixth, the QT interval increases with age, and this is true for both men and women.\[19\] Usually, men have shorter QT intervals compared to women at the same age, but QT intervals are similar between men and women in the post-menopausal years.\[19\]

Normal aging is associated with a reduced autonomic response to stress, including decreased baroreflex buffering and depressed heart rate variability.\[21\] There is an increase in the prevalence of orthostatic hypotension and supine hypertension with age; however, the presence of baroreceptor and autonomic failure is abnormal.\[22\] Because of these alterations, the cardiac electrophysiological changes that occur with age reduce the margin of functional reserve and render the aging heart more susceptible to the development of electrophysiological abnormalities. In addition, the age-related cardiac changes which include ventricular hypertrophy, senile amyloidosis, cardiac valvular degenerative changes and annular calcification, fibrous infiltration of the conduction system, and loss of natural pacemaker cells could also have profound direct and indirect effects on the development of arrhythmias.
In the atria, the ultra-rapid delayed rectifier K+ currents (I_{Kur}) are enhanced.[27] Since I_{Kur} is atrial-specific, the upregulation in I_{Kur} may render the aging atria more susceptible to the development of atrial fibrillation.[30] In the sinus node, there is significant age-related electrical and structural remodeling in the form of downregulation of sodium channels,[31] L-type calcium channels,[32] and connexin-43,[33] as well as an increase in fibrosis.[34] These ionic changes may lead to the development of sinus node dysfunction in the elderly patient.

Aging has also been shown to be associated with a downregulation in the mRNA expression of HCN4, which encodes I_{f},[35] but reduced I_{f} current has not been demonstrated. In addition, the aging myocardium is associated with abnormal intracellular Ca^{2+} regulation as expression of the SERCA-2 Ca^{2+} pump is reduced[36,37] while that of the sodium-calcium exchanger is increased.[38] This is very important because the electrical and structural remodeling of the aging heart suggest that the therapeutic targets of antiarrhythmic drugs, i.e., the cardiac ion channels, change with age. In addition to these age-related alterations in the ionic channels, the pharmacokinetics and pharmacodynamics of antiarrhythmic drugs also vary with age.

5 Changes in antiarrhythmic drug pharmacokinetics with age: Drug-body interactions

Pharmacokinetics is defined as the handling of a drug within the body, including its absorption, distribution, metabolism, and elimination. A number of age-related physiological changes that occur with aging may affect drug disposition in the body (Figure 2).

![Figure 2. Age-related changes in pharmacokinetics of antiarrhythmic drugs. Diagrammatic representation of age-related changes in the absorption, distribution, metabolism, and elimination of antiarrhythmic drugs. GI: gastrointestinal; GFR: glomerular filtration rate; CrCl: creatinine clearance; ↔: unalter; ↑: increase; ↓: decrease.](http://www.jgc301.com; jgc@mail.sciencep.com | Journal of Geriatric Cardiology)
5.1 Absorption

With age, there is a decrease in gastric acid secretion that may reduce the dissolution of tablets and the solubility of basic drugs.\[^{39}\] Antiarrhythmic drugs are weak bases, so there may be reduced gastric solubility with age, but the effects are small. The gastric emptying rate is somewhat delayed as there is reduced gastrointestinal motility, decreased mucosal surface area, and reduced splanchnic blood flow, which decreases by 30%–40% between ages 20 and 70.\[^{40,41}\] Despite these changes, the oral absorption of antiarrhythmic drugs is not significantly affected by aging, probably because most of these drugs are absorbed passively.\[^{39,42}\] However, bioavailability can be significantly affected by the decrease in first-pass intestinal wall/hepatic extraction with aging, resulting in enhanced systemic bioavailability for drugs such as propranolol and lidocaine.\[^{43,44}\]

5.2 Distribution

Drug distribution can be profoundly affected by some of the physiological changes that occur as patients get older. Between ages 20 and 70, body fat as a proportion of body weight rises from 18% to 36% in males and from 33% to 45% in females, while there is an overall reduction in lean body mass of 20% in men and 12% in women during those years.\[^{39,45,46}\] These changes significantly increase the volume of distribution of fat soluble drugs like amiodarone. At the same time, there is a reduction of 8% in total body water, thereby reducing the volume of distribution for water soluble drugs like digoxin.\[^{47}\]

In addition, the serum level of α-1-glycoprotein, which binds weak bases such as antiarrhythmic drugs, increases in the elderly, causing a reduction in the free fraction of the drugs and in the effective volume of distribution while simultaneously increasing drug plasma concentration.\[^{48}\] Plasma albumin tends to be reduced in the elderly.\[^{49,50}\] Weakly acidic drugs, such as warfarin, normally bind to albumin. Thus, the reduced plasma albumin may result in a more intense drug effect with age, making the elderly patient more susceptible to bleeding complications.\[^{42}\]

5.3 Metabolism

Drugs are metabolized in the liver by two types of reactions, namely phase I oxidative reactions and phase II conjugative/synthetic reactions.\[^{51}\] Most phase I reactions are mediated by cytochrome P450 (CYP) monoxygenases.\[^{52}\] Table 2 shows the five CYP isozymes that are important for the metabolism of clinically relevant antiarrhythmic drugs. CYP2D6 and CYP3A4 in particular are two of the most important isozymes for the metabolism of drugs, including antiarrhythmics.\[^{42,52,53}\] Quinidine, disopyramide, lidocaine, mexiletine, flecainide, propafenone, amiodarone, verapamil and metoprolol are all dependent on the activities of these enzymes for metabolism. After the age of 30, there is a 1% per year decline in liver blood flow and liver mass, correlating with a significant age-related reduction in phase I reactions.\[^{54–56}\] In contrast, the activities of phase II reactions, through which an acetyl group or a sugar is conjugated to the drug to enhance its polarity, water solubility and hence excretion via the kidneys, are relatively unaffected by age.\[^{54,57}\] Nevertheless, the reduction in liver function may reduce the clearance and increase the half-lives of antiarrhythmic drugs metabolized by the liver, such as quinidine, propafenone, amiodarone. The reduction in hepatic blood flow with age is also known to significantly reduce the clearance of high hepatic extraction ratio drugs, such as lidocaine and propranolol, which require dose adjustments according to age to minimize the risk of adverse effects.\[^{58–62}\]

### Table 2. Clinically important cytochrome P450 (CYP) isozymes and substrates.

<table>
<thead>
<tr>
<th>CYP Isozyme</th>
<th>Substrates</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP1A2</td>
<td>Mexiletine, Phenytoin, Citalopram, Theophylline, Fluoxetine</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>Caffeine, Warfarin, Diazepam, Warfarin, Phenytoin</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>Caffeine, Warfarin, Diazepam, Phenytoin, Theophylline</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>CYP2D6, Mexiletine, Phenytoin, Theophylline, Theophylline</td>
</tr>
<tr>
<td>CYP3A4</td>
<td>Quinidine, Lisinopril, Lisinopril, Lisinopril</td>
</tr>
</tbody>
</table>

5.4 Elimination

Normal aging is associated with a significant reduction in kidney size as well as in the number and size of nephrons, while the proportion of sclerotic glomeruli increases. With age, glomerular filtration rate, tubular secretion, and renal blood flow decrease approximately by 0.5%, 0.5% and 1% per year, respectively, after the age of 20.\[^{42,63,64}\] Hence, in an 80-year-old patient, the loss of renal function leads to a significant accumulation of renally-cleared antiarrhythmic drugs such as digoxin, procainamide, N-acetyl procainamide (NAPA), sotalol, and dofetilide. In addition, because of the reduction in muscle mass with advancing age, serum creatinine should not be used as a marker for estimation of renal function.\[^{65}\] A serum creatinine of 1.0 is associated with a normal creatinine clearance (CrCl) for a 35-year-old patient, an adequate but reduced CrCl in a 65-year-old patient, and an abnormally low CrCl in an 85-year-old patient.\[^{66}\] An equation such as the following should be used to estimate CrCl:

\[
\text{CrCl} = \left( \frac{140 - \text{age}}{\text{wt in kg}} \right) / (72 \times \text{sCr})
\]

For women, CrCl as calculated in the equation above
should be multiplied by a factor of 0.85.

The age-related pharmacokinetic changes associated with antiarrhythmic drugs are summarized in Table 3 and show several general features. Aging is associated with reduced clearance of many antiarrhythmic drugs, resulting in an increase in drug half-lives. Maximum drug concentration may also increase, potentially augmenting the risk of drug toxicity. The volume of drug distribution also changes with age and depends on whether the drug is lipophilic or hydrophilic. Thus, most antiarrhythmic drugs will need dosage adjustments in the elderly patient.

Table 3. Age-related pharmacokinetic changes with antiarrhythmic drugs.

<table>
<thead>
<tr>
<th>Drug</th>
<th>( t_{\text{max}} )</th>
<th>( C_{\text{max}} )</th>
<th>( t_{1/2} )</th>
<th>Vd</th>
<th>CL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digoxin</td>
<td>↑</td>
<td>NA</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Disopyramide</td>
<td>↔</td>
<td>↑</td>
<td>↑ ↔</td>
<td>NA</td>
<td>↓</td>
</tr>
<tr>
<td>Quinidine</td>
<td>NA</td>
<td>NA</td>
<td>↑ ↔</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>↑ ↔</td>
<td>↑</td>
<td>↑ ↔</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Mexiletine</td>
<td>↔ ↔</td>
<td>↑ ↔</td>
<td>↑ ↔</td>
<td>NA</td>
<td>↓</td>
</tr>
<tr>
<td>Flecainide</td>
<td>NA</td>
<td>NA</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Propafenone</td>
<td>NA</td>
<td>↑ ↔</td>
<td>↑ ↔</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Sotalol</td>
<td>↔</td>
<td>↑</td>
<td>↑ ↔</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Dofetilide</td>
<td>↑</td>
<td>↑</td>
<td>↑ ↔</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>NA</td>
<td>NA</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Dronedarone</td>
<td>↔</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Verapamil</td>
<td>↑ ↔</td>
<td>↑</td>
<td>↑ ↔</td>
<td>←</td>
<td>↓</td>
</tr>
</tbody>
</table>

\( t_{\text{max}} \): time to maximum plasma concentration; \( C_{\text{max}} \): maximum plasma concentration; \( t_{1/2} \): half life; Vd: volume of distribution; CL: clearance; NA: not available; ↔: unaltered; ↑: increase; ↓: decrease.

6 Changes in pharmacodynamics of antiarrhythmic drugs with aging: Drug-disease interactions

Pharmacodynamics is defined as the effects of the drugs on the body. The physiological changes associated with aging can profoundly affect drug pharmacodynamics and make the elderly patient more susceptible to potential adverse effects of antiarrhythmic drugs. Aging is associated with reduced cardiac reserve, rendering the heart more susceptible to heart failure. Baroreceptor sensitivity is blunted, increasing the risk of orthostatic hypotension. There is reduced sensitivity to agonists and antagonists, causing a decreased response to adrenergic drugs. Deterioration in sinus and AV nodal function in the elderly increases the propensity for developing significant bradycardia and heart blocks. Also, the increase in sensitivity to anticoagulating agents heightens the risk of bleeding in the elderly patient.

Specifically, pertaining to antiarrhythmic drugs, the age-related changes in pharmacodynamics include reduced sensitivity to blockers as well as increased sensitivity to Class I antiarrhythmic drugs in terms of sinus nodal function and electrical impulse conduction. Antiarrhythmic drugs have greater avidity in binding to cardiac tissue in patients with ischemic heart disease and cardiomyopathy. Finally, impaired homeostatic mechanisms increase the risks of potential adverse drug effects such as orthostasis, urinary retention, constipation, falls, and bleeding.

Some of the important antiarrhythmic drug-disease interactions in geriatric patients are listed in Table 4. Most antiarrhythmic drugs are negative inotropic agents. Disopyramide, flecainide, and sotalol are known to cause acute decompensation in patients with poor ventricular function. Class I antiarrhythmic drugs, blockers, and \( \text{Ca}^{2+} \) channel blockers can precipitate heart block or sinus bradycardia in the elderly. Sotalol and propafenone are blockers and can exacerbate bronchospasm. Since lung function declines throughout adult life even in healthy persons and may accelerate after age 70, elderly patients are more vulnerable to such adverse effects. Disopyramide has anticholinergic properties and is known to worsen symptoms of prostatism, which is prevalent in elderly men. In the presence of hypokalemia, digoxin can exacerbate the development of life-threatening ventricular arrhythmias. Due to reduced renal function, elderly patients are more susceptible to developing digitalis toxicity. Class I antiarrhythmic drugs in patients with coronary artery disease and myocardial infarction are pro-arrhythmic and may cause sudden death. These conditions are more common with advanced age, precluding the use of these medications in many elderly patients. Lastly, antiarrhythmics with vasodilator properties, such as procainamide, quinidine, and sotalol, can exacerbate orthostatic hypotension and precipitate falls in the elderly.

Table 4. Important antiarrhythmic drug-drug interactions in elderly patients.

<table>
<thead>
<tr>
<th>Underlying disease</th>
<th>Drugs</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHF</td>
<td>Disopyramide, flecainide, sotalol</td>
<td>Decompensation</td>
</tr>
<tr>
<td>Cardiac conduction disorders</td>
<td>Class I drugs, ( \beta ) and ( \text{Ca}^{2+} ) blockers</td>
<td>Heart block</td>
</tr>
<tr>
<td>COPD</td>
<td>Sotalol</td>
<td>Bronchospasm</td>
</tr>
<tr>
<td>Prostate hypertrophy</td>
<td>Disopyramide</td>
<td>Urinary retention</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>Digoxin</td>
<td>Arrhythmias</td>
</tr>
<tr>
<td>CAD</td>
<td>Class I drugs, ( \beta ) and ( \text{Ca}^{2+} ) blockers, quinidine, procainamide</td>
<td>Proarrhythmia, Falls</td>
</tr>
</tbody>
</table>

CHF: congestive heart failure; COPD: chronic obstructive pulmonary disease; CAD: coronary artery disease.
7 Issues with polypharmacy: Drug-drug interactions

In addition to the above, polypharmacy is an important problem in the elderly. Both the prevalence of adults with prescriptions and the number of prescriptions per person increase with age. More than 75% of elderly people in the community use one or more medications, with an average of eight prescriptions per elderly patient.90

The pervasiveness of polypharmacy makes the elderly vulnerable to adverse drug-drug interactions, including those involving antiarrhythmic drugs. Class I antiarrhythmic drugs are all sodium channel blockers, but many of them, especially the Class IA drugs, also have potassium channel blocker effects, including blockade of $I_{to}$, $I_{kr}$, and $I_{Ks}$.84,92 The potassium channel blocker effects confer the QT prolonging properties of these drugs, which are known to be associated with torsade de pointes.93 The Class IC drugs have also been shown to block $I_{to}$, which may account for their comparative effectiveness in treating atrial arrhythmias.84,92 In addition, the Class IA drugs have vagolytic effects as well as adrenergic receptor blocking effects. Propafenone is a propranolol analog and has weak blocker properties. All of these “off-target” effects of Class I antiarrhythmics may cause important adverse consequences when these drugs accumulate.

All Class I antiarrhythmics except procainamide are metabolized in the liver by CYP3A4 or CYP2D6.94 Procainamide is acetylated in the liver to form NAPA and is subsequently excreted by the kidneys through active tubular secretion, which can be inhibited by cimetidine and trimethoprim. Quinidine is metabolized by CYP3A4, but it is also a potent inhibitor of CYP2D6 and has complex interactions with propafenone metabolism.95 Drugs that inhibit the CYP system, such as cimetidine, ketoconazole, and macrolide antibiotics, also inhibit clearance of Class I antiarrhythmic drugs. Grapefruit juice inhibits intestinal wall CYP3A4 and CYP1A2 and potentiates the effects of drugs that are cleared by these enzymes.96 On the other hand, rifampin, glucocorticoids, phenytoin, ethanol, and phenobarbital induce CYP3A4, which increases quinidine, disopyramide, amiodarone, lidocaine, and verapamil clearance. Quinidine, amiodarone, and dronedarone are inhibitors of P-glycoprotein, which is required for renal excretion of digoxin, thereby augmenting digoxin levels.97

Class III antiarrhythmic drugs are potassium channel blockers, but amiodarone and dronedarone are promiscuous, inhibiting the voltage-gated sodium channel, the L-type Ca$^2+$ channel, and β-adrenergic receptors.84,92 Amiodarone and dronedarone are hepatically metabolized, while sotalol and NAPA are eliminated by the kidney. Although dofetilide is mostly cleared by the kidney, 20% is metabolized by CYP3A4, so its level can be altered by drugs, such as ketoconazole, that modulate CYP3A4 activities. Also, cimetidine inhibits renal cationic secretion of dofetilide and prolongs its half-life.98 Other agents that inhibit renal cationic secretion may have similar effects. Amiodarone is a potent inhibitor to a number of drug metabolizing enzymes and drug transporters, including CYP3A4, CYP2C9, and P-glycoprotein. Hence, the substrate of these enzymes, which include a variety of drugs commonly used in the geriatric population, will need appropriate dose adjustment when used concomitantly with amiodarone.99

Adenosine has a very short half-life and is removed by cellular uptake. Its effects are augmented by dipyridamole, which blocks adenosine deaminase, allowing adenosine to accumulate extracellularly. Theophylline counteracts the effects of adenosine by potentiating intracellular cAMP. Hence, when using adenosine, it is crucial that the patient is not taking dipyridamole or theophylline, which will profoundly alter the effects of adenosine.100-102 Digoxin is a Na/K pump inhibitor and is an inotropic agent that activates the Na/Ca exchanger, leading to an increase in intracellular Ca$^{2+}$.87 Digoxin is removed via the kidney and its secretion is mediated by P-glycoprotein. Thus, drugs such as quinidine that inhibit P-glycoprotein cause an increase in digoxin levels.97 The dose of digoxin should be adjusted based on the other drugs that the elderly patient is taking and plasma levels of digoxin should be monitored. A recent prospective cohort study of 2030 elderly patients showed that the risk of digoxin toxicity requiring hospitalization is increased more than four-fold in those with a history of recent hospitalization (within two months).88 This underscores the prevalence of medication misadventures in the elderly population, which imposes a significant burden on the health care system.103 and the importance of paying close attention to evaluate adherence, prescribing, and adverse drug reactions in the management of elderly patients’ medical care.

8 Summary

To conclude, what do we need to know about antiarrhythmic drug therapy in elderly patients? The first thing to know is the patient population. Elderly patients are avid consumers of medications, which increases the risk of drug-drug interactions. Moreover, the elderly are subject to significant age-related physiological changes that may alter the effects of individual drugs. The second thing to know is the antiarrhythmic drugs. Age-related alterations in drug

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pharmacokinetics, in hepatic metabolism, and in renal elimination can be pronounced for some drugs and are often under-appreciated. The third thing to know is that the use of antiarrhythmic drugs in elderly patients must be individualized. Potential drug-drug and drug-disease interactions are common and must be scrutinized for each patient. All these issues may have a significant impact on the health-related quality of life in the elderly.

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