Anti-Arrhythmic Drugs

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Abstract

Anti-arrhythmic drugs (AAD's) alter the electrical properties of the heart principally by either prolonging the cardiac action potential, decreasing conduction velocity, reducing focal automaticity or a combination of these effects. Despite the fact that a large number of AAD's were initially developed for ventricular arrhythmias the most common current indication is currently atrial fibrillation (AF).

Although the majority of these drugs act relatively specifically on certain targets or receptors, the overall general distribution of these receptors throughout the ventricular and atrial myocardium may result in unwanted effects such as Torsades de Pointes (TdP) predominantly with class IA and class III drugs, and prolongation of AV conduction, QRS widening and monomorphic VT with class IC drugs. The toxicity profile of AADs is varied, leading to severe adverse effects and discontinuation of treatment in 12–19% of patients. Therefore, the choice of AAD must depend on the presence of comorbidities, cardiovascular risk and patient preference, proarrhythmic potential, toxic effects, and symptom burden.

A meta-analysis of 44 trials involving 11,322 patients showed that all AAD's were associated with an increased risk of proarrhythmia with the exception of amiodarone and propafenone (Lafuente-Lafuente et al. 2006). Although amiodarone is a very useful agent in the treatment of both atrial and ventricular arrhythmias its use is often limited as a result of its potential for long-term non-cardiac side effects (Rothenberg et al. 1994).

More recently, "atrial selective" AAD's have been developed which may have improved efficacy with better side effect profile. Additionally, some drugs (such as renin-angiotensin aldosterone inhibitors and anti-inflammatory agents) may affect the underlying substrate and be indirectly antiarrhythmic.

Mechanisms of Action: An Overview

Although the majority of AAD's have multiple effects on either the AP directly or by autonomic modulation, their actions can generally be classified into groups according to the predominant

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mechanism or resulting electrophysiological effect. This classification is called the Vaughan Williams system which was subsequently modified by Singh and Harrison (Table 10.1). It should be remembered that most AAD's have properties belonging to more than one group; it is therefore more appropriate to refer to 'classes of antiarrhythmic drug action', rather than to drugs belonging to a particular class.

Drugs with Class I action act by blocking the rapidly activating sodium channels that are responsible for phase 0 of the AP thus affecting its slope and amplitude. These drugs are subdivided according to the rate of binding and dissociation from the sodium channel. Class IB mechanism of action is associated with the most rapid onset of action and dissociation, IA has intermediate activities and IC the slowest (Fig. 10.1).

These variances in action result in clinically relevant differences as a function of heart rate - drugs with the slowest rates of binding and unbinding have "rate dependent properties" with the effect of greater slowing of conduction velocity (manifest on the surface ECG as greater degree of QRS prolongation) at higher heart rates, not seen with the class 1b mechanism of action. As well as their effects on the slope of rapid depolarization, agents with class I properties also have different effects on repolarization (and APD) and thus refractory periods. Class IA property is generally associated with an increase, Class IB with a shortening and Class IC with no effect on the APD.

Class II agents act by blocking beta adrenergic receptors, antagonizing the effect of circulating, neurally or locally released catecholamines, with effects on all cardiac tissues. Additionally, they prolong the phase 2 and 3 (after chronic use) of the AP and thus lengthen the effective refractory period.

Agents with Class III properties such as sotalol and amiodarone prolong the APD principally by inhibition of the potassium channels (although these drugs also have other electrophysiologic properties-see below).

Class IV action inhibits the slow calcium current and therefore depress phase II and III of the AP in certain tissues primarily the SAN and AV nodes).

Antiarrhythmics with Class IA Properties

Procainamide is conjugated to the active metabolite N-acetylprocainamide at a rate determined by whether the patient is a rapid acetylator (Jusko et al. 1980; Atkinson and Ruo 1986). Although it was previously used for the treatment of atrial and ventricular arrhythmias its use is now largely reserved for the treatment of VT. It is also used for the acute management of haemodynamically stable, pre-excited AF in the WPW syndrome (Class IIb indication) (Fuster et al. 2006). Proarrhythmia occurs in up to 9% of cases (Podrid et al. 1987) and like all class IA drugs its

Table 10.1 Classification of current anti-arrhythmic drug actions as well as inotropic effects on the ventricle and potential pro-arrhythmic effects

Class	Examples	Mechanism	Inotropic Effect	Pro-arrhythmia
Ia	Procainamide Quinidine	Inhibition of Intermediate Na^+ Channel	Negative	QRS Widening and VT (Torsades)
Ib	Lidocaine Mexilitine	Inhibition of fast Na^+ Channel	Negative	Asystole
Ic	Flecainide, Propafenone	Inhibition of slow Na^+ Channel	Negative	1:1 AV Conduction of atrial atrial arrhythmias slowed by the drug
II	B Blockers	B Adrenoceptor Blockade	Negative	Bradycardia
III	Amiodarone Sotalol	K^+ Channel Blockade	Neutral	Sotalol: Bradycardia, ↑QT, Torsades
IV	Ca Channel Blockers	Ca^{2+} Channel Blockade	Negative	Bradycardia

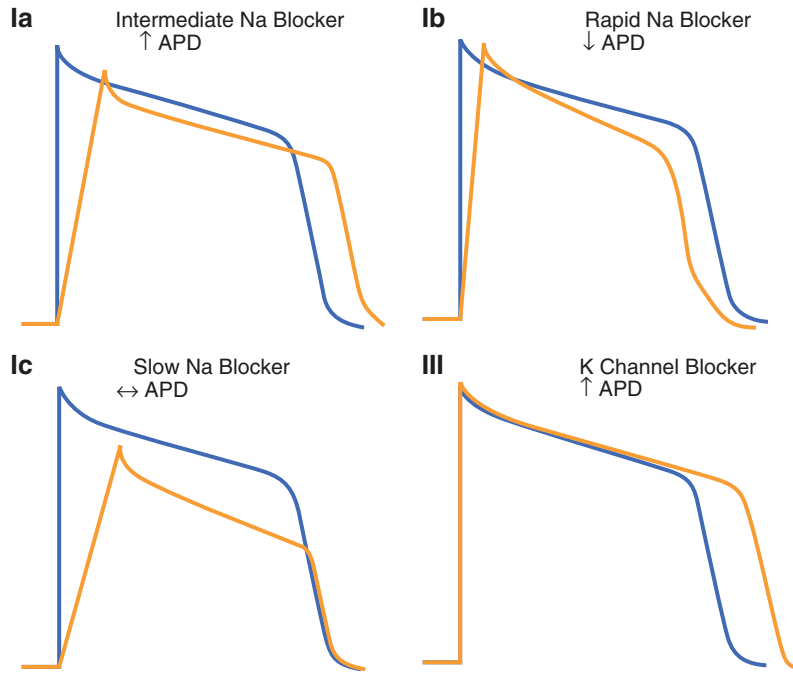

Fig. 10.1 Schematic of the effects of Class Ia, Ib, Ic and Class III effects on the Cardiac AP

use has been severely restricted due to the associated risk of TdP particularly in patient with bradycardia and left ventricular hypertrophy (LVH) (Yap and Camm 2003). In general terms the risk of TdP for all class IA and some class III AAD's include a long baseline QT interval, a family history of Td, female gender, bradycardia, renal impairment (for renally excreted drugs) and a low potassium or magnesium (Camm 2008).

Procainamide can also increase the ventricular rate in patients with uncontrolled AF or flutter (Class IA effect). This occurs as a result of slowing the fibrillation or flutter rate as well as increasing the likelihood that a given impulse will pass through the AV node due to the direct vagolytic action of procainamide. Thus, conduction through the AV node must be slowed and the ventricular response controlled before therapy with procainamide is initiated in these disorders. Nearly all patients will develop a positive antinuclear antibody, with a lupus-like syndrome in approximately one-third of patients taking the drug for more than 1 year (Brogan and Olsen 2003). Severe neutropaenia has been reported with long term use of oral procainamide (Katkov and Ellrodt 1985). In patients with structural heart defects, evidence suggests that procainamide may be more effective than lidocaine in the termination of monomorphic VT, although further reports are still lacking (Komura et al. 2010). It is also commonly used for pharmacological testing in Brugada risk stratification.

Quinidine has similar properties and side effects to procainamide, but owing to its additional effect on the transient outward current, there has been some limited interest in this drug in patients with Brugada syndrome. Although there is some evidence to support a degree of efficacy in maintaining sinus rhythm following an electrical cardioversion for AF (Coplen et al. 1990) it carries significant pro-arrhythmic side effects with an increased associated mortality (Reimold et al. 1992). The incidence of TdP reported with quinidine use varies from 0.5% to 8% (Grace and Camm 1998) and like all class IA drugs the QT prolongation tends to occur early and therefore it is recommended that it should be initiated in the hospital under continuous ECG monitoring (Thibault and Nattel 1999). Modest QT prolongation is relatively common while excessive prolongation is unusual and generally indicates toxicity. As with all AAD's

in this group, it is contraindicated in the presence of structural heart disease and LVH and is not recommended as first-line agent for the long-term management of any atrial arrhythmia. One of the more common reasons for discontinuation of the drug are the associated gastrointestinal side effects such as nausea, reduced appetite, an abnormal bitter taste and abdominal discomfort are relatively common occurring in approximately one third of patients. Quinidine has been reported to be effective in patients with ventricular tachycardia (Viskin et al. 2019) and Brugada syndrome (Belhassen et al. 2004), as well as with idiopathic ventricular fibrillation (Tsai et al. 1998).

Disopyramide has marked anticholinergic effects and thus in theory may prove useful in vagally mediated AF (Fuster et al. 2006). The evidence for disopyramide in AF however is very weak involving a small study involving 90 patients following a successful electrical cardioversion from AF to sinus rhythm (Karlson et al. 1988). Following 1 month 70% of patients receiving disopyramide were in sinus rhythm versus 39% in the placebo group. It is considered a second- or third-line agent for suppression of atrial and ventricular arrhythmias and conversion of AF to normal sinus rhythm. Due to its negative inotropic effect it has been used in the treatment of hypertrophic cardiomyopathy in order to reduce the outflow tract gradient and improve symptoms (Pollick 1982) Other than the proarrhythmic and negative inotropic effects characteristic to this group the other main adverse effects are related to its anticholinergic effects, including urinary retention, blurred vision, constipation and dry mouth. This drug is therefore rarely used clinically.

Antiarrhythmics with Class IB Properties

The two main drugs in Class IB are lidocaine and mexiletine both of which act predominantly on the ventricular myocardium.

Lidocaine is a short acting intravenous antiarrhythmic which has been used extensively for the management and prophylaxis of ventricular arrhythmias. The initial clinical data for the use of lidocaine was in its ability to suppress PVC's and prevent VF after an acute myocardial infarction (Lie et al. 1974). However this practice was halted after data showed an associated increased mortality most likely related to bradyarrhythmias and hypotension (MacMahon et al. 1988). Although one trial has shown an increased prehospital survival with lidocaine (Herlitz et al. 1997) other randomised trial comparing lidocaine with amiodarone have shown amiodarone to be superior in terms of return of spontaneous circulation (Dorian et al. 2002) as well as a lower rate of asystole (Weaver et al. 1990). As a result of this the ALS (UK) guidelines recommend the use of lidocaine only as an alternative if amiodarone is not available.

Mexiletine is structurally similar to lidocaine but has a much higher oral bioavailability and therefore, is available as an oral preparation. Its main activity occurs in the His Purkinje and ventricular myocardium with minimal effects on the sinus node, atrium and AV node (Roos et al. 1976; McCornish et al. 1977). The most frequent side effects are related to GI disturbances and CNS toxicity. Cardiovascular side effects include hypotension, sinus bradycardia, and worsening of ventricular arrhythmias in 10–15% of cases (McCornish et al. 1977). Use of mexiletine has been reported to be associated with an increased mortality (Campbell 1987) but may be used in patients who cannot tolerate amiodarone; or in combination with amiodarone in electrical storm.

Class IC AAD's

The class IC drugs flecainide and propafenone have the slowest onset of action in sodium inhibition and have no direct effect on action potential duration.

Current guidelines recommend flecainide as a first-line agent for the conversion of existing AF and prevention of recurrences in patients with intermittent episodes of AF, in patients without structural heart disease. Although its use in this subset of patients is well-established, its clinical

use continues to be limited predominantly due to the potential risk of ventricular proarrythmia (Preliminary report 1989). The exact mechanism underlying flecanide's ventricular proarrhythmic potential remains unknown.

Cardiac arrhythmia is more likely in the presence of myocardial ischaemia, suggesting that it may be due to excessive conduction slowing in ischemic tissue. Both flecainide and propafenone have been shown to be relatively similar in terms of efficacy in the management of symptomatic paroxysmal AF in two randomized control trials (Chimienti et al. 1996; Aliot and Denjoy 1996). However, a recent meta-analysis of randomized studies found the overall AF conversion rate within 2 h to be higher with the use of flecainide (66%) when compared with any other antiarrhythmic agent (46%) (Markey et al. 2018). Indeed, in cases of recent onset AF, IV flecainide has been shown to be effective in termination of the arrhythmia in 90% of cases (Fernández-Martinez et al. 2000). Oral flecainide has been shown to be as effective as the intravenous preparation for acute chemical cardioversion although obviously with a slower onset of action (Alp et al. 2000).

This fact combined with the large degree of use dependence has led to the regimen called 'pill in the pocket' (PiP) in which patients with symptomatic paroxysmal AF self-administer a single oral dose of flecainide (generally with a beta blocker or rate slowing calcium blocker) for chemical cardioversion. Although this has been shown to be effective in up to 94% of cases with no significant adverse effects (Alboni et al. 2004), this strategy has only been employed in highly selected patients who can reliably self-identify symptomatic episodes and is not ideal for many patients with paroxysmal AF. In general, if this strategy is to be used, patients are usually tested with the identical regimen in hospital to assess for side effects and potential arrhythmias. Despite this precaution, 5% of patients still experience problems such as presyncope, syncope and sinus arrest.

Despite the efficacy of class IC drugs, their use has been largely limited by safety concerns. They may occasionally convert AF to atrial flutter with 1:1 AV conduction and thus result in a paradoxical increase in ventricular response rate. This tachycardia occasionally can be confused with VT particularly when there is QRS widening (also due to the drug). Given that they have minimal effects on AV conduction, it is recommended that they be used in the presence of an AV nodal blocker such as a beta blocker. However, the major concerns regarding these drugs arose from a series of trials showing an increase in cardiovascular mortality in patients with ventricular arrhythmias in the setting of coronary artery disease and other structural heart disease. The Cardiac Arrhythmia Suppression Trial (CAST) compared flecainide, encainide, moricine and placebo for the suppression of PVC's in 1498 post MI patients (Preliminary report 1989). The trial was prematurely terminated after showing an increased mortality in patients receiving flecainide and encainide (subsequently withdrawn) primarily due to the incidence of arrhythmias.

Although propafenone may have a relatively better side effect profile given its additional beta adrenergic blocking effects, the Cardiac Arrest Survival in Hamburg (CASH) study showed a significant increase in mortality in patients receiving propafenone. The CASH trial was designed to compare survival with an ICD as compared to antiarrhythmic drug therapy with amiodarone, propafenone or metoprolol, in 349 survivors of cardiac arrest due to documented VT (Kuck et al. 2000).

For these reasons, these drugs are contraindicated in the setting of prior myocardial infarction or a history of VT, and relatively contraindicated in the setting of structural heart disease.

Class II Antiarrhythmics

This class of drugs act by inhibiting sympathetic activity, primarily via beta-adrenergic blockade, and is subdivided based on the specific adrenergic blockade profile and associated properties. Propranolol is a first-generation non-selective beta-blocker with equal affinity for the β1 and β2 receptors. At high doses, propranolol may also block sodium channels. Despite its proven effi-

cacy in reducing ventricular rate in AF, propranolol has not been shown to be useful as an atrial anti-arrhythmic (Tsolakas et al. 1964).

Metoprolol and bisoprolol are second-generation beta-blockers, which preferentially inhibit β2 receptors and may have more useful atrial antiarrhythmic effects than propranolol. Bisoprolol has been shown to be similar to sotalol in the maintenance of sinus rhythm at 12 months following an electrical cardioversion (Plewan et al. 2001). Metoprolol has also been shown to be superior to placebo in maintenance of sinus rhythm as well as a slower ventricular rate during a recurrence (Kuhlkamp et al. 2000).

Beta adrenergic blockers have been shown to reduce mortality owing to a reduction in arrhythmic death in most cases, in patients with long QT syndrome (Sauer et al. 2007), survivors of cardiac arrest (Hallstrom et al. 1991), post myocardial infarction (Freemantle et al. 1999) and in patients with impaired LV systolic function (McAlister et al. 2009).

Class III

Class III AAD's exert their action by blocking potassium channels, thereby prolonging repolarization, the APD, and the refractory period. These changes are manifested on the surface ECG by prolongation of the QT interval. This group includes sotalol, amiodarone, dofetilide, vernakalant and ibutilide.

Sotalol consists of 2 isomers, D and L, each of which contribute to its antiarrhythmic properties. The D isomer blocks the rapid component of the delayed rectifier potassium current (IKr channel) during phase 3 of the AP and thus prolongs the AP duration. The L isomer also prolongs the cardiac AP, while having a degree of beta-adrenergic blocking activity. Although a preparation of the D isomer has been developed, it has been shown to be associated with an increase in the risk of mortality in patients with impaired LV function and a recent MI or heart failure with a history of prior MI (Waldo et al. 1996).

Sotalol has been shown to be effective in maintaining sinus rhythm and reducing the incidence of episodes of AF, although not as effectively as amiodarone. The CTAF study randomised patients with a history of AF to sotalol, amiodarone or propafenone (Roy et al. 2000). After a mean follow-up of 16 months similar percentages of patients receiving sotalol and propafenone had a recurrence of AF while significantly fewer receiving amiodarone experienced AF recurrences.

In clinical practice, sotalol is generally used for the control of paroxysmal AF as a second- or third-line agent after flecainide/propafenone and amiodarone. It has also been shown to reduce the recurrence of sustained ventricular arrhythmias (Mason 1993), albeit less than amiodarone (Connolly et al. 2006), and can also be considered after amiodarone in terms of reducing ICD discharges.

The most significant risk associated with sotalol is the risk of TdP particularly at slower heart rates, which has been reported as approximately 2.5% at a median follow up of 164 days (Lehmann et al. 1996) This risk is increased in females, patients with a history of heart failure, patients with renal impairment and at high doses of sotalol (greater than 320 mg/day) (Lehmann et al. 1996).

Amiodarone was first used as an anti-anginal drug in the 1960's, and its anti-arrhythmic properties were first reported in 1970. The predominant mode of action is class III by blocking the IKr and IKs channels. This results in a reduction in dispersion of refractoriness, re-entry and pro-arrhythmia and overall a prolongation of myocardial repolarization homogeneously. Additionally, it also blocks sodium channels (Class I effects) and thus reduces conduction velocity, has non-selective beta adrenergic blocking effects (Class II) and inhibits the L type calcium channel (Class IV). It causes use dependent potassium channel blockade meaning that as the heart rate increases the refractory period increases incrementally (Singh et al. 1994).

The onset and mode of action depends on the type of administration. If given intravenously the onset of action is several hours and there is minimal AP prolongation except in the AV node. The oral preparation takes several days and the

overall effects are more pronounced after chronic usage.

Amiodarone has been shown to be the most efficacious AAD in the treatment of both AF and VT. The Canadian Trial of AF, in which patients with at least one episode of AF were randomized to various antiarrhythmic medications, showed that 35% of patients randomized to amiodarone had a recurrence of AF versus 63% of patients randomized to either sotalol or propafenone (Waldo et al. 1996). There was no significant difference in the maintenance of sinus rhythm between those who received either sotalol or propafenone. Given its multichannel effects and minimal negative inotropic effects, it is considered relatively safe in patients with impaired LV function and is recommended as first line therapy for the treatment of ventricular arrhythmias unless there is a contraindication (MacMahon et al. 1988). Although amiodarone prolongs the QT interval the risk of torsades de pointes VT is less than 1% (Goldschlager et al. 2007).

The most common and significant side effects which limit the long-term use of amiodarone are generally non cardiac, with adverse effects reported as high as 15% within the first year of treatment and 50% during long term therapy (Goldschlager et al. 2007). It is therefore important that the patient is monitored for side effects as shown in Fig. 10.2.

Amiodarone induced hypothyroidism is more common than thyrotoxicosis. Within the first 3 months of therapy there is an increase in thyroid stimulating hormone (TSH), free T4 and a reduction in free T3. TSH then normalises while T4 and T3 may remain abnormal. The importance of this is that it is generally not useful to check thyroid function within the first 3 months and following this the most useful measure is TSH (Goldschlager et al. 2007). Amiodarone induced thyrotoxicosis is less predictable and can occur relatively suddenly at any time during treatment. It can be due either to aggravation of pre-existing thyroid disease or thyroiditis, although often it is difficult to distinguish between these. It is generally recommended that all patients being commenced on long term amiodarone therapy should have baseline TFT's which should be rechecked after 3 months to establish a new baseline and then every 6 months or sooner if clinically indicated (Goldschlager et al. 2007).

Lung toxicity has been reported as occurring in up to 2% of patients (Goldschlager et al. 2007). Risk factors for pulmonary fibrosis are a prior history of lung disease and a daily dose of amiodarone greater than 400 mg/day (Vassallo and Trohman 2007). It may present anytime from 1 week following initiation of the drug and is relatively unpredictable. Therefore, although pulmonary function tests are frequently performed, they are of limited value in this case.

There is no conclusive evident that pulmonary functions tests are useful in anticipating or diagnosing amiodarone long toxicity. However, close clinical surveillance for symptomatic adverse effects of amiodarone is critical in order to detect the early onset of neurological symptoms including vivid dreams, tremor, postural instability, incoordination.

These and other non cardiac side effects of amiodarone have subsequently led to the development of the noniodinated benzofuran derivative, dronedarone.

The dose of dronedarone was established in the Dronedarone Atrial Fibrillation Study after Electrical Cardioversion (DAFNE) (Touboul et al. 2003). Three different doses (800, 1200, or 1600 mg) of dronedarone daily were compared with placebo in patients following a successful electrical cardioversion. A dose of 800 mg/day delayed the time to recurrence of AF; 35% dronedarone versus 10% placebo at 6 months. While higher doses of dronedarone resulted in better ventricular rate control in patients who converted to atrial fibrillation, higher doses were also associated with increases in the QT interval albeit with no cases of torsades de pointes. Additionally, dronedarone administered at any dose was not associated with any thyroid, pulmonary or ocular side effects. The most important side effects associated with the use of dronedarone were gastrointestinal disturbance. Based on these results, the dose of 400 mg twice daily was chosen and was subsequently studied in patients with either atrial fibrillation or atrial flutter in the twin studies called The European Trial in Atrial Fibrillation or Flutter Patients Receiving

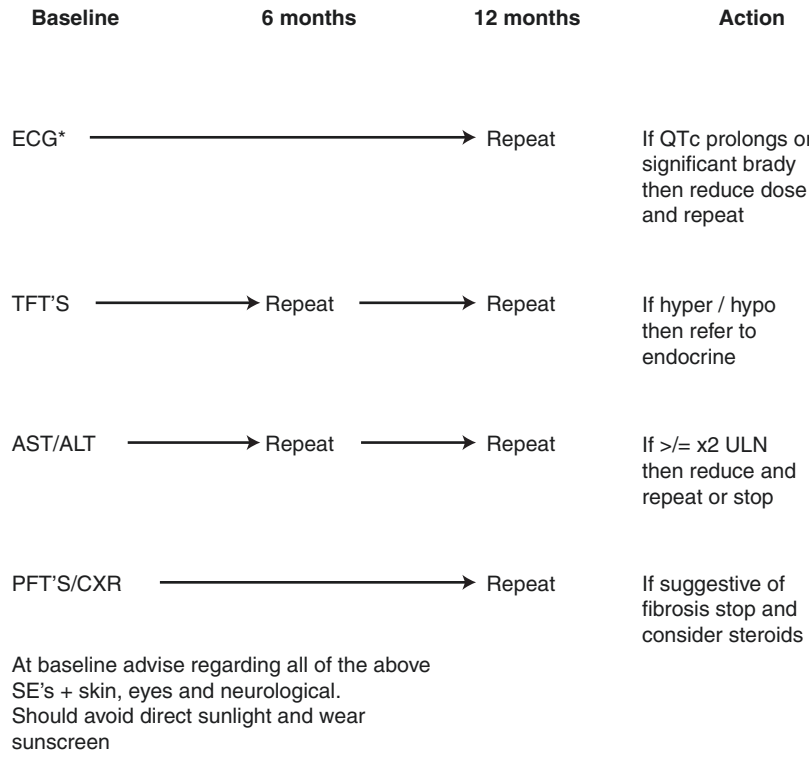

Fig. 10.2 Suggested Monitoring for the Side Effects of Long Term Amiodarone (*Evidence of QTc prolongation, sinus node or AV node conduction abnormalities should prompt close monitoring)

Dronedarone for the Maintenance of Sinus Rhythm (EURIDIS) and the American- Australian-African Trial with Dronedarone in Atrial Fibrillation or Flutter Patients for the Maintenance of Sinus Rhythm (ADONIS) (Singh et al. 2007). These trials randomised patients with a history of paroxysmal atrial fibrillation or atrial flutter to receive either dronedarone or placebo. Dronedarone increased the time to first recurrence of atrial fibrillation from 53 to 116 days, when patients receiving placebo were compared to those administered dronedarone. Furthermore, in patients who had a recurrence of atrial fibrillation dronedarone significantly reduced the ventricular rate. A post hoc analysis revealed a 27% reduction of relative risk of hospitalization and death with dronedarone treatment.

The effect of dronedarone in ventricular rate control for patients with permanent AF was studied in the Efficacy and Safety of Dronedarone for Control of Ventricular Rate (ERATO) (Davy et al. 2008). The addition of dronedarone (800 mg/day) to standard rate-control therapy reduced the ventricular rate by 11.7 beats/min after 2 weeks of treatment and by a mean of 24.5 bpm during exercise.

Dronedarone was studied in patient with moderate to severe left ventricular impairment irrespective of the rhythm in the Antiarrhythmic Trial with Dronedarone in Moderate-to- Severe Congestive Heart Failure Evaluating Morbidity Decrease (ANDROMEDA) (Kober et al. 2008). Patients had a left ventricular ejection fraction less than 35% and had been hospitalized with new or worsening heart failure. In addition, they also needed to present with at least one episode of shortness of breath on minimal exertion or at rest (NYHA III or IV) or paroxysmal nocturnal dyspnoea within the month prior to admission. There was no restriction related to renal function.

After a median follow up period of 2 months, a significantly higher mortality rate was reported with dronedarone treatment (8.1%) as compared with placebo (3.8%). Worsening left ventricular function corresponding with a higher the risk of death and has led to the avoidance of dronedarone in patients with severe LV dysfunction and heart failure.

To help address some of these issues a further study was carried out looking at patients with stable AF and at least one cardiovascular risk factor. The Assess the Efficacy of Dronedarone for the Prevention of Cardiovascular Hospitalization or Death from Any Cause in Patients with Atrial Fibrillation/Atrial Flutter (ATHENA) (Hohnloser et al. 2009) had the composite primary end point of all-cause mortality and cardiovascular hospitalization. 4628 patients with a history of paroxysmal or persistent AF/atrial flutter were randomised to dronedarone 400 mg twice a day versus placebo with 12 months of follow-up. The use of dronedarone was associated with a significant 27% reduction in the primary end point of death or cardiovascular hospitalization. The most frequently reported adverse effect of dronedarone was gastrointestinal, principally nausea and diarrhoea that led to drug discontinuation in several cases. The overall reduction in hospitalisations was a principle reason for dronedarone gaining clinical approval in North America and more recently, led to a second draft guidance by the National Institute for Clinical Excellence (NICE). A recent retrospective analysis comparing patients receiving a first prescription of dronedarone versus other AADs (amiodarone, flecainide, propafenone, or sotalol) found that patients receiving dronedarone was associated had a decreased risk of myocardial infarction and stroke (Ehrlich et al. 2019). These results are consistent with DATA from post hoc studies of the ATHENA trial, which correlated dronedarone administration to a reduced risk of first acute coronary syndrome and stroke as compared to placebo (Connolly et al. 2009; Pisters et al. 2014). It is therefore recommended that dronedarone should be administered as second-line treatment in patients with additional cardiovascular risk factors whose AF has not been controlled by first-line therapy (usually including beta blockers).

Class IV

Verapamil and diltiazem block the L-type calcium channel and principally prolong the atrioventricular nodal refractory period. The VERDICT study showed no benefit in maintenance of sinus rhythm of verapamil over digoxin (Van Noord et al. 2001). Two large trials which examined the use of verapamil in the maintenance of sinus rhythm following an electrical cardioversion both showed verapamil combined with quinidine was similar in efficacy to sotalol with a higher incidence of TdP in the sotalol group (Patten et al. 2004; Fetsch et al. 2004). Due to its negative inotropic effects verapamil should be used cautiously in patients with left ventricular dysfunction. Additionally, verapamil should also be avoided in sick sinus syndrome as it suppresses sinus node automaticity. Both verapamil and diltiazem are similar in efficacy and side effects (other than constipation associated with verapamil). Calcium channel blockade may be a reasonable choice of drug for ventricular rate control in patients with preserved LV function and can be considered as an alternative to ß-blockers.

AAD's Not in the Vaughan Williams Classification

Some drugs such as digoxin, adenosine and ivabradine do not fit into the traditional Vaughan Williams classification.

Digoxin acts directly on the myocardium in order to increase the concentration of intracellular sodium and exert its positive inotropic effects. However, in addition to its vagotonic effects, this may shorten the atrial effective refractory period and therefore increase its potential to develop AF in patients who are in sinus rhythm (Sticherling et al. 2000). Its predominant role in AF is therefore to slow AV conduction (through its vagotonic effects) and thereby reduce the ventricular rate. It is not an ideal drug for acute ventricular rate control as the onset of action is 4–6 h and may not be as effective if the rate is partially sympathetically driven. Data consistently suggests that it may have deleterious effects and therefore it is relatively used as a monotherapy. Nonetheless, it continues to have an important role in the management of AF and is particularly effective when combined with a beta-adrenergic blocker due to

synergistic effects (Fuster et al. 2006). Most recently, data based on the outcomes of the AF-CHF trial found that digoxin use amongst patients with combined heart failure and reduced ejection fraction and AF was associated with increased all-cause mortality (Elayi et al. 2020).

Adenosine is a metabolite of adenosine triphosphate which results in slowing of AV nodal conduction, shortening of the atrial myocardial refractory period and depression of sinus node automaticity (Lerman and Belardinelli 1991). Adenosine is highly effective in terminating supraventricular arrhythmias in which the AV node forms part of the reentrant circuit, such as in the cases of AV nodal reentry and orthodromic reciprocating tachycardia.

Additionally, it can be used for diagnostic purposes such as transiently slowing AV conduction in SVT to identify the underlying rhythm and may also be helpful in differentiating SVT from VT (although very rarely adenosine may terminate a specific type of VT). Side effects such as facial flushing (due to cutaneous vasodilation), dyspnoea, and chest pressure have been reported to occur in about 30% of patients (Platia et al. 1990). Given the short half-life of adenosine, these side effects generally last less than 60 s. The downside to this short duration of action is that in some cases, arrhythmias recur after several minutes following termination with adenosine (DiMarco et al. 1985).

Ivabradine is a novel selective inhibitor of the I_f channel in the SA node, therefore reducing the sinus rate with no effect on either the AV node or intraventricular conduction times (Di Francesco and Camm 2004). Although its principle use is for symptom relief in patients with chronic stable angina, it may also have a clinical role in patients with an inappropriate sinus tachycardia. A recent study examining its use in 18 symptomatic patients with an inappropriate sinus tachycardia (defined as a nonparoxysmal tachyarrhythmia with a P-wave morphology and endocardial activation identical to sinus rhythm and an excessive increase of heart rate in response to minimal physical activity and emotional stress, and nocturnal normalization) showed a significant reduction in heart rate on Holter and exercise stress tests (Calo et al. 2010). Despite the study's small sample size, there may be a role for this drug in these patients where other drug therapies can be relatively ineffective and ablation therapy may carry significant risks.

The Future: Novel AAD's

Given the significant cardiac and non-cardiac side effects associated with current AAD's there has been a huge interest in the development of novel 'atrial selective' drugs for the treatment of AF. These drugs can be broadly divided into amiodarone derivatives such as dronedarone, PM101 and budiodarone; selective Iks blockers such as HMR1556; atrial repolarization-delaying agents such as vernakalant; and sodium channel blockers such as ranolazine.

Atrial Repolarization Delaying Agents: Vernakalant

Vernakalant is a relatively new anti-arrhythmic drug which works by predominantly targeting early-activating K+ channels and frequency-dependent Na+ channels in the atria. It has showed efficacy and safety in recent-onset AF, demonstrating an efficacy of 52% in the acute conversion of recent onset AF compared to a 4% success rate with placebo (Roy et al. 2008). More recently, the results of the randomized double-blind multicentre AVRO trial showed that vernakalant has a higher efficacy for the conversion of AF as well as a greater rate of symptom relief (51.7% converted with vernakalant versus 5.2% with amiodarone) in 254 adult patients with AF. Treatment with vernakalant resulted in a rapid conversion to sinus rhythm, with a median conversion time of 11 min. Most recently, a large meta-analysis of 1358 participants comparing vernakalant to another drug or placebo for the

pharmacological cardioversion of AF deemed vernakalant a viable first-line treatment option for patients with haemodynamically stable recent-onset AF without severe structural heart disease (McIntyre et al. 2019). While the authors raised moderate concern over suspected publication bias, vernakalant appeared to be well tolerated and relatively safe with no cases of ventricular arrhythmias or drug related deaths. The main side effects associated with its use appear to be dysgeusia (30%), transient sneezing (17%), hypotension (5%) and bradycardia (5%). Currently, the use of vernakalant is approved in Europe and Canada and is indicated in patients with AF (⩽7 days) and no heart disease (Class I, level A) or in patients with mild or moderate structural heart disease (Class IIb, level B). Vernakalant may also be considered for recent-onset AF (⩽3 days) following cardiac surgery (class IIb, level B).

Sodium Channel Blockers: Ranolazine

Ranolazine has been shown to be effective as an anti-anginal agent when added to standard medical therapy most likely through various mechanisms but predominantly through its ability to inhibit the inward sodium current. In a similar mechanism it has been postulated that this may have anti-arrhythmic effects in the atria where rapid atrial rates during AF may result in oxidative stress and atrial myocardial ischaemia. The Metabolic Efficiency with Ranolazine for Less Ischaemia in Non-ST-elevation acute coronary syndrome— Thrombolysis in Myocardial Infarction (MERLINTIMI 36) trial compared ranolazine with placebo in 6560 patients hospitalized with acute coronary syndromes. A significant reduction in tacharrhythmias (SVT and VT) was noted on 7-day continuous cardiac monitoring in patients commenced on ranolazine versus placebo (Scirica et al. 2007). There was no effect on sustained arrhythmias such as AF and VT and no overall effect on mortality or recurrent ischaemia. Further clinical studies are required to assess the clinical utility of ranolazine as an AAD.

Important Points

1. Anti-arrhythmic drugs alter the electrical properties of the heart principally by either prolonging the cardiac AP (thus prolonging refractoriness), decreasing conduction velocity, reducing focal automaticity or a combination of these effects.
2. The Vaughan Williams classification categorizes anti-arrhythmic drugs action into groups according to the main mechanism of action. These are:

Class I action block the fast sodium channels which are responsible for phase 0 of the action potential thus affecting its slope and amplitude. These drugs are subdivided according to the rate of binding and dissociation from the sodium channel. Class IB mechanism of action is associated with the most rapid onset of action and dissociation, IA has intermediate activities and IC the slowest.

Class II action block beta adrenergic receptors prolonging the phase 2 and 3 (after chronic use) of the action potential and thus lengthen the effective refractory period.

Class III action refers to prolongation of the action potential duration, principally by inhibition of the potassium channels.

Class IV action inhibits the slow calcium current and therefore depress phase II and III of the AP in certain tissues primarily the SN and AV nodes).

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