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Therapeutic Drug Monitoring of Anti-Arrhythmic Drugs: Enhancing Safety and Efficacy in Clinical Practice

Bhavana U*, Rishitha K, Gomini B and Shravani Y

Omega College of Pharmacy, Affiliated to Osmania University, India

***Corresponding author:** Bhavana U, Omega College of Pharmacy, Edulabad, Ghatkesar, Hyderabad, Telangana, India, Email: ubhavanavaishnavi23@gmail.com

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Abstract

Therapeutic drug monitoring (TDM) is a clinical pharmacokinetics technique that involves determining plasma drug concentrations and adjusting dosages to maintain them within a targeted therapeutic window. It is useful for drugs with a narrow therapeutic index, which are the only ones that require TDM. TDM is necessary for about 50-60 substances and considers factors like patient compliance, bioavailability, serum drug level, rate of elimination, drug access to the receptor site, and receptor sensitivity. When clinical response and medication concentration are well correlated, TDM is highly useful. Regular TDM can also be used to evaluate treatment failure due to non-compliance. Therapeutic drug monitoring (TDM) is crucial for ensuring the safe and effective use of antiarrhythmic drugs, which can have significant toxicities. TDM helps optimize dosing, minimize adverse effects, and improve therapeutic outcomes by monitoring drug levels in the blood. Antiarrhythmic drugs like amiodarone, sotalol, lidocaine, and flecainide need to be closely monitored to effectively manage arrhythmias while lowering toxicity. TDM helps maintain plasma drug concentrations within a therapeutic range, balancing effectiveness and safety. It can assist in adjusting pharmaceutical dosages, identify early toxicity warnings, and allow dose adjustments before severe side effects. TDM is not always necessary for all agents, but can be used more broadly to customize antiarrhythmic treatment, particularly for high-risk individuals. In conclusion, Future advancements in pharmacogenetics and analytical techniques are expected to enhance the accuracy and usefulness of TDM, thereby enhancing its personalization. For example, quinidine has a toxicity starting at 3μg/ml, while procainamide has early toxicity at 8 to 10μg/ml. Disopyramide has an effective range of 2.5 to 6.0μg/ml, while lignocaine has an effective range between 1.5 and 5.5μg/ml. Mexiletine has a very low therapeutic index. However, challenges such as lack of therapeutic ranges and potential pro-arrhythmic effects need to be addressed to fully realize the benefits of TDM in anti-arrhythmic therapy.

Keywords: Therapeutic Drug Monitoring; Anti-Arrhythmic Medications; Cardiac Arrhythmias; Pharmacogenetics; Drug Half-Life; Drug Toxicity Monitoring; Cardiac Safety; Adverse Drug Reactions; Polypharmacy; Dose Adjustments; Narrow Therapeutic Index

Abbreviations

TDM: Therapeutic Drug Monitoring; ADRs: Adverse Drug Reactions; DART: Direct Analysis in Real Time; VW: Vaughan-Williams; NAPA: N-Acetylprocainamide; MEGX: Monoethylglycine Xylidide; GX: Glycine Xylidide; DLIS/DLIF: Digoxin-Like Immunoreactive Substances/Factors; ERP: Effective Refractory Period; ECG: Electrocardiographic; DART-MS/MS: Direct Analysis in Real Time-Mass Spectrometry; EIA: Enzyme Immunoassay; FPIA: Fluorescence Polarization Immunoassay.

Introduction

Therapeutic drug monitoring (TDM) is vital for optimizing anti-arrhythmic drug therapy, ensuring both efficacy and safety by maintaining drug concentrations within a therapeutic range. Given the potential toxicities of these medications, TDM plays a crucial role in dose optimization, minimizing adverse effects, and improving therapeutic outcomes. Drugs with a narrow therapeutic index and high pharmacokinetic variability particularly benefit from TDM.

Anti-arrhythmic agents have well-defined plasma concentration ranges, below which they are ineffective and above which they pose significant toxicity risks. Additionally, active drug metabolites can influence both efficacy and adverse effects. While modern technologies enable easy detection of these metabolites, their clinical relevance, especially for substantial levels of compounds like N-acetyl procainamide, remains uncertain.

TDM helps prevent concentration-dependent adverse drug reactions (ADRs) and ensures patient compliance. For instance, the effective plasma concentration range for propafenone spans from 40 to over 3,000ng/mL, whereas amiodarone ranges between 500 and 2,500 ng/mL. Among available analytical techniques, Direct Analysis in Real Time (DART) offers a promising rapid analysis method by eliminating chromatographic separation, reducing overall analytical time, and requiring minimal solvents. As an ionization technology compatible with various mass spectrometers, DART is widely applied in pharmaceuticals, forensics, healthcare, and material sciences. Its potential for quantitative TDM analysis extends to drugs like tacrolimus and methotrexate, paving the way for more efficient drug monitoring solutions [1].

Objectives of TDM for Anti-Arrhythmic Drugs

TDM optimizes anti-arrhythmic drug efficacy while minimizing adverse effects, especially for drugs with narrow therapeutic windows and significant toxicity.

It aids in monitoring patient compliance and detecting toxicity, especially for drugs like amiodarone and digoxin, which overlap their therapeutic and toxic ranges, ensuring careful monitoring to prevent digitalis intoxication [2].

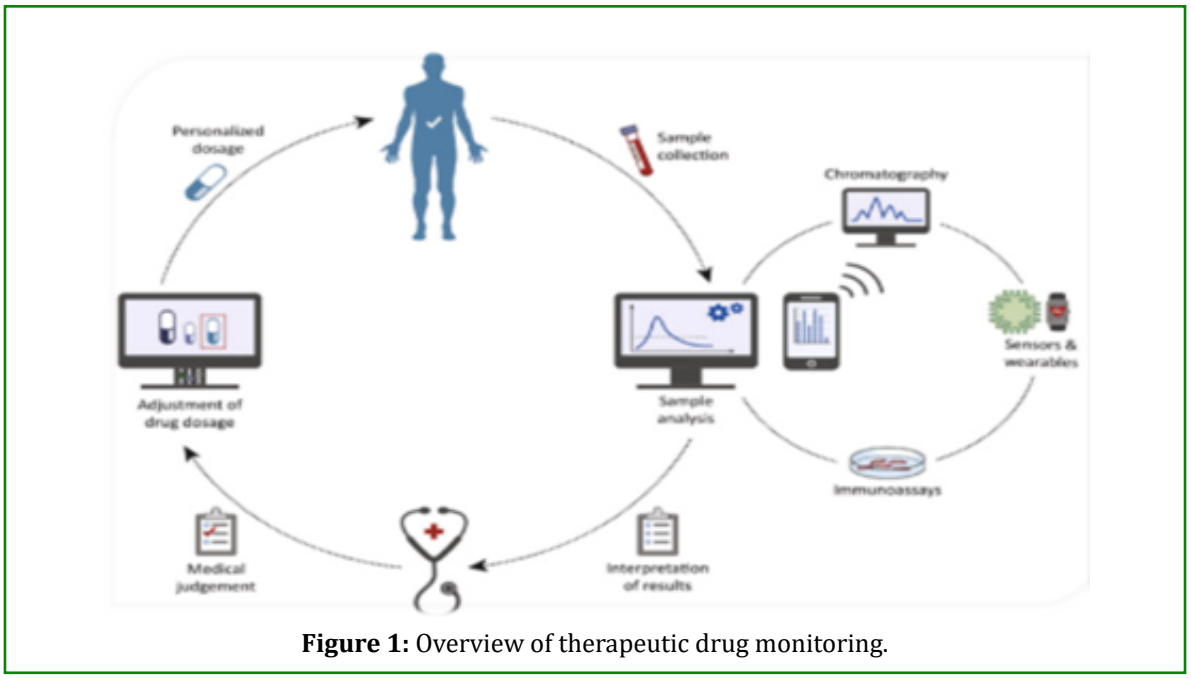

Figure 1: Overview of therapeutic drug monitoring.

TDM requires the active management of free drug concentrations in human bodily fluids via chromatographic or immunoassay-based approaches, as well as on-site solutions {sensors and wearables} to maximise the benefit to each particular patient.

Determining the Drug's Plasma Concentrations for TDM

Reliable, sensitive, and specific assays for the drug of interest are necessary to establish concentration-efficacy-toxicity relationships. In addition to being free from interference from endogenous substances and other drugs taken at the same time, assays must be able to distinguish between the main drug and any active or inactive metabolites. Examples of drugs with both active (like procainamide's metabolite N-acetylprocainamide) and inactive (like mexiletine) metabolites are provided in this article. Assays in the past relied on colorimetric, spectrophotometric, and fluorometric techniques, each of which had progressively lower levels of specificity [3]. The majority of attempts to demonstrate concentration-effect correlations were therefore either unsuccessful or of questionable quality. However, by combining these detection techniques with chromatographic resolution, TDM has been firmly established as a beneficial adjuvant to effective medication administration. However, once incorporated into labs that conduct assays on a large number of specimens and usually use less experienced analysts, the potential for increased accuracy and repeatability is rarely realized. Commercial immunoassay kits, such as fluorescence polarization immunoassay (FPIA) or enzyme immunoassay (EIA), provide the basis for the most common routine operations.

Classification of Anti-Arrthymic Drugs

The most often used classification scheme for AADs is the Vaughan-Williams (VW) method. AADs affect the action potential, are categorized by channel, and affect the parameters (AV conduction, QT, and sinus node function) in an EP study. Despite the fact that anti-arrhythmic pharmacology is often arranged according to mechanisms of action, further investigation has uncovered a variety of processes within classes. Crucially, digoxin, ivabradine, and ranolazine—three well-known antiarrhythmic medications—are not included in this method. These three medications have been included in other updated versions of the VW categorization scheme [4].

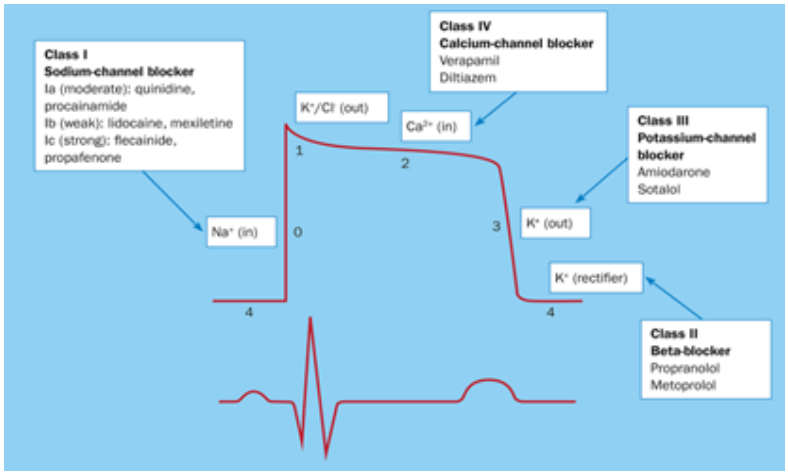

Figure 2: Drugs affecting cardiac action potential.

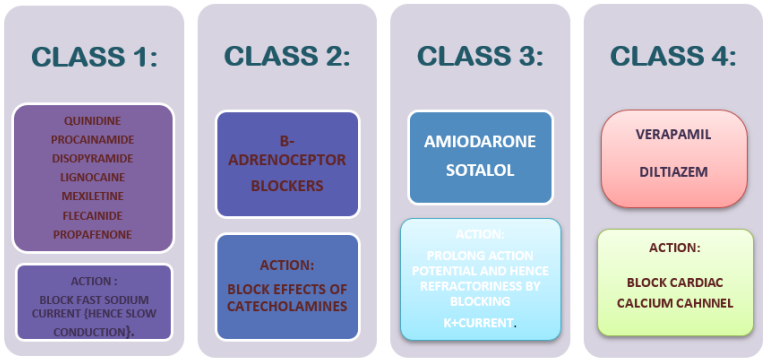

Figure 3: Vaughan williams the classification of anti-arrhythmic drugs, into four groups based on their mechanism of action.

AADs were divided into four groups by Singh-Vaughan Williams: beta-adrenoceptor antagonists (Class II), Na+ channel blockers (Class I), medications that mainly block K+ channels and extend the duration of cardiac action potentials (APD) without altering intracardiac conduction (Class III), and non-dihydropyridine L-type Ca2+ channel blockers (Class IV). Subsequently, Class I AADs were separated into medications with slow (IC), rapid (IB), and intermediate (IA) offset kinetics of blocking Na+ channels. Because it is easy to grasp and facilitates discussion of the possible advantages and disadvantages of AADs, this classification is frequently utilized [5].

Class I Antiarrhythmic Agents: The bulk of traditional antiarrhythmic medications fall into this group, which is the oldest and biggest. The fast inward sodium current, which causes the upstroke and rapid conduction of the cardiac action potential, can be blocked by these substances. They can therefore postpone or even stop intracardiac conduction entirely. As a result, when recent large-scale mortality trials revealed that some of these drugs can both cause and prevent dysrhythmias, many practitioners were not shocked. The prevalence of 'prodysrhythmia' has become widely acknowledged, leading to a significant decline in the usage of these medications, especially in Europe and Australasia [6].

Class IA Drugs (Quinidine, Disopyramide and Procainamide): Both in vitro and in vivo, these medications—quinidine being the most commonly used—have remarkably similar electrical characteristics. At concentrations in or near the therapeutic range, they block the outward potassium currents that cause the cardiac action potential to repolarise as well as the inward sodium currents, which is a common activity of all Class I agents. As a result, they can cause proarrhythmic complications via both conduction slowing and the promotion of oscillatory behaviour of the action potential associated with delayed repolarisation, resulting in a type of polymorphic ventricular tachycardia known as 'torsade's de pointes'. Class IA medicines (disopyramide, which blocks both K+ and Na+ channels) are rarely used to prevent AF and other arrhythmias nowadays. Flecainide and propafenone, both class IC medicines (strong Na+ channel blockers with beta-blocker characteristics), are modestly effective. These medications can be used safely in people who do not have ischaemic heart disease or heart failure with a reduced ejection fraction (HFrEF). Propafenone also possesses beta-blocking properties, which may exacerbate baseline bradycardia and conduction problems. When given at ≥160 mg daily, sotalol acts as a beta-blocker and also blocks Class III K+ channels. Patients with pre-existing bradycardia require additional monitoring, especially as proarrhythmia (torsades de pointes) occurs more frequently at lower heart rates (reverse usage dependency) [7].

Quinidine: Quinidine is frequently used orally in a number of long-acting forms, such as gluconate or sulphate. Quinidine gluconate or sulphate has an elimination half-life of 5 to 8 hours. Nonetheless, commonly used sustained release formulations retain adequate plasma concentrations for a minimum of eight hours. After a dosage change, a new steady state is reached at least 24 to 36 hours after starting therapy with such a sustained release formulation. TDM and dosage alterations should consider trough levels measured 8-12 hours after the initial dose. Dosage modifications should not be adjusted more than once every 2-3 days. FPIA or EIA are now the most widely used methods for determining quinidine plasma level [8]. Fluorometric assays were used in the early stages of development because to the drug's intrinsic potent fluorescence, although they are nonspecific. While the data appear to be somewhat accurate, the introduction of H.P.L.C. assays resulted in basically improved specificity.

Protein binding ranges from 70 - 80 percent and the liver metabolises 80 percent of the medication. Urine contains the remaining substance, unaltered. Renal excretion occurs by glomerular filtration and is pH dependant. Renal clearance of quinidine may be reduced with higher urine pH and decreased creatinine clearance, and so decreases in the elderly. Quinidine does not respond to peritoneal or haemodialysis. Bioavailability varies amongst patients, required a final daily dose of 400-1200 mg/day to achieve therapeutic plasma concentrations. For these reasons, therapeutic medication monitoring is highly recommended. The range of therapeutic plasma levels is 3–8 μg/ml. This range, which mostly relates to the compound's effectiveness in lowering ectopic activity, does not correlate well with the dose-response curve for torsades de pointes, a particular form of quinidine toxicity, as was previously highlighted. In fact, the danger of torsades de pointes and action potential prolongation is highest at the lower end of the therapeutic range, and it can happen at concentrations lower than this.

Disopyramide: Disopyramide can be administered intravenously or orally. Peak plasma levels appear one to two hours following oral bioavailability, which is around 80%. The typical daily oral dosage is 300–600 mg. In healthy people, disopyramide has a half-life of four to six hours. The half-life lengthens when creatinine clearance declines, and elimination is mostly renal [9,10]. Usually, between 50 and 80 percent of the drug is excreted unchanged in the urine. One metabolite has 24 times the parent's anticholinergic potency and may contribute to anticholinergic side effects, although several others are unlikely to have an antiarrhythmic effect. There are effective and accessible long-acting versions of disopyramide. Disopyramide concentrations in the therapeutic range are roughly 2.8-7.5μg/mL. Disopyramide's protein binding has nonlinear, saturable characteristics, in contrast to the majority of other antiarrhythmic drugs. α1-

acid glycoprotein, which is increased in acute illnesses such myocardial infarction, is bound by disopyramide. Along with these cautions, as with quinidine, there is a link between low plasma concentrations of disopyramide and a significant risk of torsades de pointes.

Procainamide: Usually, 3-6 g of procainamide are used orally each day. Bioavailability is high, and peak plasma concentrations are attained 1-2 hours after pill delivery. The elimination half-life is brief (three to five hours), and the protein binding rate is only 10–20%. As a result, when this medication will be used for an extended period of time, long-acting forms are usually provided. Between 40 and 70 percent of procainamide is removed from urine without undergoing any changes due to glomerular filtration and active tubular secretion. About 16–30% of procainamide is acetylated by hepatic N-acetyltransferases, resulting in N-acetylprocainamide (NAPA). NAPA accounts for around 16–20% of metabolism in "slow acetylators," whereas "rapid acetylators" account for 25–30%." NAPA has minimal metabolism and is eliminated through the kidneys [11].

When monitoring procainamide medication, serum levels of both procainamide and NAPA are typically measured, which has strong antiarrhythmic activity, particularly Class III activity (prolongation of the action potential via potassium channel blocking). NAPA (but not procainamide) can be eliminated using haemodialysis and haemoperfusion, but not via peritoneal dialysis. Hepatic and/or renal disease will definitely interfere with excretion; hence the procainamide dosage should be lowered depending on TDM. Cardiac failure, which interferes with hepatic metabolism and renal function, may necessitate a dose reduction. The ratio of procainamide to NAPA in plasma will be determined by the individual's acetylator status. Slow acetylators will have a lower NAPA/procainamide ratio. Procainamide's therapeutic plasma concentration typically ranges from 4-12μg/ml. The FPIA and EIA tests are most commonly used to perform TDM of procainamide and its primary metabolite, NAPA. The antibodies are specific for both the parent and metabolite.

Class IB Drugs (Lignocaine and Mexiletine)

Lignocaine: A common parenteral treatment for ventricular tachycardias is lignocaine. Furthermore, it is increasingly being used in combination with oral drugs such as flecainide and mexiletine to treat a range of chronic pain conditions, particularly those thought to have a neurogenic origin. Lignocaine must be given parenterally due to significant hepatic first pass metabolism into potentially harmful metabolites. It has an 8-minute half-life, a plasma elimination half-life of around two hours, and a steady-state distribution volume of about 1.3 l/kg. Plasma concentrations will undoubtedly be monitored in order to minimize toxicity, particularly if the infusion is to be continued for longer than 24 hours. Therapeutic plasma values typically range from 2 to 6μg/ml. Toxicity and efficacy are often concentration dependent. The most widely used EIA and FPIA assays do not significantly cross-react with the primary metabolites, which have relatively modest plasma concentrations [12].

Lignocaine has two active metabolites: monoethylglycine xylidide (MEGX) and glycine xylidide (GX), both with short half-lives of 2 and 1 hours, respectively. The pharmacokinetics of lignocaine will be significantly influenced by old age, as well as any drug or disease state that affects hepatic blood flow and metabolism. Clinically significant examples include alcoholic liver disease, heart failure, β-adrenoceptor blockers, and cimetidine.

Mexiletine: Like lignocaine, mexiletine is efficiently absorbed after oral therapy and reaches peak plasma concentrations in two to four hours. About 80% of it is bioavailable. Oral dosages between 100 and 600 mg/day have a linear association with plasma concentration. For antiarrhythmic effects, the therapeutic range is approximately 0.6-1.7 μg ml−1; mexiletine (and flecainide) is also covered by the remark on lignocaine concentrations for chronic pain. A single dose taken orally has an average half-life of 6–10 hours, while it can be higher (11–17 hours) in those with cardiac conditions. Hepatic metabolism is the main mechanism by which mexiletine is eliminated, with 85% of it being transformed into inactive metabolites.

Renal insufficiency has no effect on the plasma kinetics of mexiletine as long as creatinine clearance is more than 10 ml/min. About 15% are excreted in the urine undamaged. The percentage of medication excreted unchanged varies with pH since urine is a weak base. The half-life of mexiletine is shorter at pH 5.0 (2.8h) than at pH 8.0 (8.0h). Dialysis does not allow for the elimination of xiletine. It has been shown that medications that induce hepatic enzymes enhance the hepatic clearance of mexiletine. These consist of rifampicin and phenytoin. Smoking cigarettes boosts mexiletine's excretion by increasing its conjugation with glucuronic acid. Atropine, morphine, and cimetidine can all prevent the intestines from absorbing mexiletine. Half-lives and maximum blood concentrations are unchanged [13].

Class IC Drugs (Flecainide, Propafenone)

Flecainide: Flecainide has a low hepatic first pass impact and is readily absorbed when taken orally. Patients with cardiovascular disease had an elimination half-life of 10 hours on average, whereas healthy people had a half-life of 7 to 15 hours. However, there is a lot of variation, thus it is advised to check the plasma concentration. Plasma flecainide levels show a linear relationship with dose over a broad range. With possible toxicity above 1000ng ml−1 and probably beyond 1600 ng ml−1, the therapeutic range is around 200–1000ng ml−1. The drug is rapidly metabolised into molecules that are far less effective than its original form. Conduction velocity depression is substantially concentration dependent, with

no exacerbating effects like quinidine or disopyramide. In fact, the 200–1000ng ml−1 therapeutic range for flecainide is based on the acetate salt rather than the free base, flecainide; hence, the range would be 175–870ng ml−1 [14].

Propafenone: One Class IC agent that has some β-adrenoceptor blocking properties is propafenone. After two to three hours, plasma concentrations peak due to the effectiveness of oral absorption. Because of the significant hepatic first-pass metabolism, the bioavailability is only 10–20%. There exist nonlinear kinetics. The half-life of plasma is around two to twelve hours. As a result, it is advised that electrocardiographic indicators (such QRS prolongation) and the extent of suppression of overt dysrhythmias be used to quantify efficacy and toxicity more precisely than plasma drug concentrations. Propafenone is classified as a racemic drug. A common method for determining plasma concentrations is H.P.L.C. For bioequivalence testing, stereospecific tests have been created and employed. Since the enantiomers of propafenone exhibit varying levels of action and the metabolite, 5-hydroxypropafenone, is antiarrhythmic and reaches clinically important levels, it might be challenging to interpret propafenone plasma concentrations. The enantiomers are similar in their ability to block sodium channels, however S-propafenone is the one with β-antagonist activity [15,16].

Class II Antiarrhythmic Agents (B-Adrenoceptor Blockers)

Clinicians tend to underestimate the substantial antiarrhythmic action of β-adrenoceptor blockers. Additionally, because of a 30% decrease in the probability of sudden death in these patients, they are the only class of antiarrhythmic drugs that have demonstrated a notable mortality reduction following myocardial infarction. As such, they constitute a crucial and underappreciated part of the physician's arsenal of antiarrhythmic tools. Nevertheless, in contrast to Class I medications, their side effects and effectiveness do not correlate well with plasma concentrations, and β-adrenoceptor blockers play little to no part in therapeutic drug monitoring.

Agent	Dose range	Frequency	Half-life	Lipo-/hydrophilic nature	Cardioselectivity
Atenolol	25–50mg	Twice daily	6–7h	Hydrophilic	Cardioselective
Bisoprolol	1.25–20mg	Once daily	10–12h	Lipophilic	Cardioselective
Carvedilol	3.125–25mg (max. 50mg if >85kg)	Twice daily	10h	Lipophilic	Non-cardioselective
Labetalol	50–400mg	Twice daily	4h	Lipophilic	Non-cardioselective
Metoprolol	50–100mg	2–3 times daily	3h	Lipophilic	Cardioselective
Propranolol	10–40mg	3–4 times daily	4h	Lipophilic	Non-cardioselective
Sotalol	40–160mg	Twice daily	10–20h	Hydrophilic	Non-cardioselective

Figure 4: List of Beta-Blocker Medications.

Class III Antiarrhythmic Agents

Sotalol: A common antiarrhythmic medication, sotalol exhibits both Class III antiarrhythmic actions and nonselective β-adrenoceptor blockage. This latter activity, which results in a dose-dependent prolongation of the ventricular action potential length, is brought on by the blocking of outward potassium currents. Additionally, it raises the risk of torsade's de pointes, which is usually linked to elevated sotalol blood levels. Hypokalaemia, which can happen with concurrent high-dose diuretics, increases this risk. With no significant hepatic first-pass metabolism, sotalol has an oral bioavailability of about 60%. Without any discernible active metabolites or substantial plasma protein binding, almost half of the oral dosage is recovered in the urine undisturbed. Consequently, the serum concentration varies somewhat. Unlike other β-adrenoceptor antagonists like propranolol and metoprolol, this medication does not exhibit polymorphic metabolism due to its lack of metabolic clearance. The half-life of plasma is quite long, ranging from 10 to 15 hours on average. Plasma concentrations are directly related to changes in creatinine clearance and vary linearly with increasing dose. Usually, sotalol is taken orally twice a day in dosages between 80 and 160 mg. More cases of Torsade's de pointes occur when daily dosages surpass 320 mg. Increasing the dosing interval to once daily is typically the first step when there is decreased renal function. If creatinine clearance is less than 10–30 ml/min, using the medication every other day can be adequate. Treatment with

sotalol does not involve any notable pharmacokinetic drug interactions. Predictable adverse effects result from sotalol's β-adrenoceptor blocking action, such as pharmacodynamic interactions with other cardioactive substances including calcium channel blockers and antiadrenergic medications, which may have extra detrimental inotropic or chronotropic effects. When combined with medications that block outward potassium currents, such as amiodarone, tricyclic antidepressants, phenothiazine, terfenadine, astemizole, and macrolide antibiotics, especially erythromycin, it may also have additive effects that slow cardiac repolarization and increase prodysrhythmia [17,18].

Amiodarone: This widely used drug, usually classified as a Class III agent, undoubtedly prolongs ventricular action potential when used in chronic doses. However, it has several other actions that could be responsible for its proarrhythmic and antiarrhythmic properties. These include mild calcium channel blockage, strong non-competitive anti-sympathetic activity, and significant sodium channel blocking (Class I action). Since the 1960s, it has been widely utilized, initially as a vascular smooth muscle relaxant for angina and then as an antiarrhythmic medication. It is currently the most often used antiarrhythmic in several nations, including Australia. Amiodarone's highly unique pharmacokinetics and undesirable side effects make its use challenging. These factors will only be touched upon here because they have already been examined in detail in recent assessments. Amiodarone's variable bioavailability (20–80%) and terminal elimination half-life of 35–40 days, which may surpass 100 days, have hindered its administration (usually by mouth). The electrophysiological characteristics of the major metabolite, desethylamiodarone, are very similar to those of the original molecule and are found in high concentrations in tissues and plasma. For one to eight weeks, clinicians usually use a loading dose of 600–2000 mg/day, followed by a maintenance dose of 200–400 mg/day.

Perhexiline: Despite being used for 25 years to treat angina pectoris, perhexiline maleate has not become very well-liked. Though its widespread use has been limited by what are thought to be unpredictable serious hepatic and neurological side effects, it does not have any significant unfavorable inotropy or hemodynamic effects. Before it was shown to block at least some outward potassium channels, it was first discovered to be a calcium antagonist. Regardless of how it works, it is now evident that toxicity is directly correlated with blood levels of perhexiline and that the drug has a genetically defined saturable rate of hepatic metabolism. Since metabolism is saturable within the typical clinical dose range, there is no correlation between plasma perhexiline levels and dose. Perhexiline's primary metabolic pathway is hepatic metabolism via CYP-2D6, which is susceptible to genetic variation, with up to 10% of the Caucasian population being 'slow metabolisers'. The dosing range for 'therapeutic' plasma concentrations is large, ranging from 50 mg per week to 600 mg/day. Maintenance doses typically range from 100-400 mg/day, with a target plasma concentration of 0.15-0.6μg/ml (0.38-1.5μm) [19]. Patients with symptomatic values in this range may benefit from cautious dosage increases to 0.6-1.2 μgml−1. Ten percent of slow-metabolizing patients will have extremely elevated blood levels following the first week of treatment. Additional TDM should be used to monitor these individuals when they are reduced to a low maintenance dosage of 50–100 mg once weekly. The remaining patients should continue taking 100 mg once daily after the first week of treatment. Next, 50–100 mg daily dose increases should be given at intervals of 2-4 weeks, based on clinical effectiveness and plasma concentration assessments.

Agent	Dosing	Adverse Effects	Drug Interactions
Flecainide (Tambocor)	50-150 mg bid; decrease by 50% if GFR ≤50 mL/min; 200-300 mg once[a]	Dizziness, tremors, HF exacerbation	Digoxin
Propafenone (Rythmol)	600 mg once[a]; IR: 150-300 mg tid; SR: 225-425 mg bid	Asthma exacerbation, dizziness	Digoxin, warfarin
Amiodarone (Cordarone, Pacerone)	1.2-1.8 g/day until 10 g total,[a] then lowest effective dose (usually 100-400 mg/day)	Hyperthyroidism, hypothyroidism, retinal deposits, pulmonary fibrosis, hepatopathy	Numerous; substrates of 3A4, 2D6, 2C9, 2C19, P-glycoprotein
Dronedarone (Multaq)	400 mg bid	Abdominal pain, worsening HF, QT prolongation	3A4 inhibitors, digoxin, statins
Sotalol (Betapace)	80-160 mg bid; 80 mg/day if CrCl 40-60 mL/min	HF exacerbation, bradycardia, bronchospasm, TDP	NA
Dofetilide (Tikosyn)	125-500 mcg bid[a] based on renal function	TDP, dizziness, diarrhea	3A4 inhibitors, verapamil, trimethoprim, hydrochlorothiazide, cimetidine

Figure 5: List of medications used to treat atrial fibrillation, their dosages, potential adverse effects, and possible drug interactions.

Digoxin: Digoxin is the cardiac glycoside that is given the most frequently. It can be administered intravenously, intramuscularly, or orally. It has a half-life of 40–150 hours and an oral bioavailability of about 75%. It is not greatly metabolized, but when renal function declines, metabolic clearance rises. Because it is removed unaltered in the urine, people with renal problems should have their dosage carefully regulated. Digoxin was one of the first agents for which routine TDM was implemented. TDM is responsible for the decrease in the occurrence of clinically significant digitalis toxicity since plasma concentration assays became widely available in the 1970s. The therapeutic and hazardous concentration ranges overlap, and toxicity can occur within the therapeutic range. Some clinical trial evidence suggests that efficacy is concentration-dependent within the therapeutic range, as well as significant evidence of concentration-dependent toxicity [20].Digoxin is mostly tested for TDM by the FPIA and EIA. Digoxin has strong cross-reactivity with its metabolites, and commonly used immunoassays may not be able to distinguish it from other medications like spironolactone and its metabolites. Because the digoxin antibodies in the assay kit compete with circulating Fab fragments for binding, digoxin assays (such as "Digi bind") are unreliable for at least 10 days after digoxin antibodies are administered to treat toxicity. A 'digoxin-like' reaction can also be triggered by endogenous molecules, commonly referred to as digoxin-like immunoreactive substances/factors (DLIS/DLIF). Variable specificity for DLIF is shown by commercial kits. DLIF may be more problematic in renal failure, hepatic dysfunction, and new-borns, with ultrafiltration reducing interference and improving specificity, although not in all specimens. A more modern monoclonal antibody assay has exhibited increased selectivity both in regarding inhibition by DLIF and digoxin metabolites, and may also provide reliable unbound quantities of digoxin in the presence of 'Digi bind'. Thus, digoxin concentrations must be interpreted with precaution in light of these potential interferences and cross reactivities, which may explain, in part, patients' varied responses even within the 'therapeutic' range of digoxin concentrations. Because digoxin functions by attaching to and inhibiting the sodium-potassium pump, hypokalaemia dramatically increases digoxin toxicity, which reduces pump activity. For digoxin-using patients, every attempt should be made to keep plasma potassium levels within normal ranges. Similarly, increased serum calcium concentrations can enhance digoxin, and vice versa. Other medications can have a major effect on digoxin serum level. It is already well established how digoxin and quinidine interact; when quinidine is given to a patient who is already taking digoxin consistently, digoxin plasma levels rise by 50–150 percent. Within hours, this rise begins to happen. Digoxin displacement from binding sites, which is sustained by a decrease in renal digoxin clearance, is one of its causes. Quinidine's suppression of the 'drug-pump' P-glycoprotein could be the main mechanism. Digoxin levels frequently rise noticeably when using other cardioactive medications such diltiazem, propafenone, amiodarone, and verapamil. Anti-adrenergic drugs have little effect on serum digoxin levels but may cause further unfavourable chronotropic effects.Multichannel blockers include amiodarone and dronedarone. Therefore, with the introduction of these medications, patients who already have bradycardia and/or AV conduction anomalies should be closely observed both clinically (symptoms) and electrocardiographically. AAD frequently causes bradycardia, sinus node dysfunction, and anomalies in AV node conductivity. Due to AV nodal effects, sotalol, dronedarone, and amiodarone may all lower heart rate during AF.

Drug	Mechanism of Action	Channels Effected	Dosing	Contrain-dications	Sideeffects/ Considerations
Class I—Sodium Channel Agents					
Class IA					
Quinidine	Blocking rapid inward sodium depolarisation in a use-dependent fashion and extending repolarisation by blocking the delayed rectifier potassium channel in a reverse-use-dependent fashion.	INa, Ito, IKr, M, α	PO only: Sulphate 300 mg-max tolerated q6h-q12h; gluconate 324-648 mg q8h-q12h.	Severe AV node dysfunction, thrombocytopenia or underlying platelet dysfunction. Prolonged QT.	At therapeutic levels, can cause pro-arrhythmia.
	Slowing Phase 4 depolarization during spontaneous automation.				At therapeutic levels, it can lead to arrhythmias.
	The net effect is an increase in action potential duration at fast heart rates, a prolonged effective refractory period (ERP), and decreased automation.				Can prolong QT.

Procainamide		INa, IKr	IV: 10–17 mg/kg; PO: 500–1000 mg q6h	Severe AV node dysfunction, underlying Systemic Lupus	Drugs can cause Systemic Lupus Erythematosus.
					Therapeutic doses may produce agranulocytosis, that requires CBC monitoring.
				Erythematosus.	Degrades into the hazardous metabolite 'NAPA', which requires monitoring, particularly when used in IV formulations.
					Can lead to negative inotropy and hypotension.
				Prolonged QT.	At therapeutic levels, can promote arrhythmia.
					Can extend QT.
Disopyramide		INa, Ito, IKr, IK(ATP), M	PO only: 150 mg q6h	Severe AV node dysfunction.	Causes negative ionotropy and hypotension. hypertension.
					At therapeutic levels, can cause pro-arrhythmia.
					Significant anticholinergic side effects.
					Can prolong QT.
Class IB					
Lidocaine	Use dependent blockage of the inward sodium depolarisation current to decrease the maximal velocity of depolarisation.	INa	IV only: 1 mg/kg bolus followed by 1–3 mg/min	Severe AV node dysfunction.	CNS adverse effects like seizures, coma, or death requiring frequent blood level monitoring.
Mexiletine	Decreased action potential and ERP duration, lowering the automaticity of phase 4 depolarisation.	INa	PO: 150 mg q8h.	Severe AV node dysfunction.	Increased risk of drug-induced liver injury.
					Can develop tremors and ataxia.
					High risk of gastrointestinal distress.
Class IC					

Flecainide	The most effective of the inward sodium blocking drugs, significantly lowering action potential conduction velocity in atrial, ventricular, and specialised conduction tissues.	INa, IKr, and Ikur	PO only: 50-200 mg q12h (may increase to q8h).	Structural heart disease or reduced ejection fraction.	At therapeutic levels, it may cause arrhythmias.
					Blocking appears use-dependent, with minimal impact on action potential duration or ERP.
	Blocking occurs in a use-dependent manner, with minimal impact on overall action potential duration or ERP.				PR and QRS prolongation.
Propafenone		INa, IKr, IKur, β, α	PO only: IR release 150–300 mg q8h; ER release: 225–425 mg q12h	Structural heart disease or reduced ejection fraction.	May cause atrial arrhythmias to slow, leading to hazardous 1:1 conduction.
Class II—Beta Blockers					
Propranolol	Blunting sympathetic activity on cardiac tissue, most notably by decreasing phase 4 depolarisation, thereby decreasing automaticity via decreased conduction velocity and increased ERP within the AV-node, minimising reentry.	β1, β2, Ina	IV: 1–3 mg boluses q5min, PO: 10–160 mg q6h–q12h	Severe AV node dysfunction, Sick Sinus Syndrome.	Can result with severe bradycardia and stimulate cardiogenic shock.
Metoprolol		β1	IV: 5mg q5min ×3, PO: Tartrate 12.5–200 mg q6h–q12h, Succinate 12.5–200 mg q12h–q24h		
Nadolol		β1, β2	PO only: 40–320 mg qDay		
Carvedilol		β1, β2, α	PO only: 3.125–25 mg q12h		
Class III—Potassium Channel Agents					
Amiodarone	Mostly by blocking the delayed rectifier potassium channel, which effectively prolongs repolarisation and increases the ERP, reducing the risk of re-entry.	INa, ICa, IKr, IK1, IKs, Ito, β, α	IV: 150–300 mg bolus, 0.5–1 mg/min (1 mg/min for 6 h then 0.5 mg/min for 18 h), PO: initial 400 mg q12h then taper to as low as 100 mg q24h if needed	Pre-existing thyroid, liver, and pulmonary diseases.	TSH and LFT levels must be monitored annually for thyroid/liver toxicity.
					PFT monitoring must be performed on annually for pulmonary fibrosis.
	Amiodarone exhibits mechanisms with other anti-arrhythmics, including vasodilation and negative inotropic effects.				Photosensitivity may develop on the skin.
					Can induce corneal micro deposits, impairing eyesight.

Sotalol	Sotalol is a racemic combination of d- and l-sotalol with distinct pharmacologic effects, including class II (nonselective ß-blocker) characteristics. Profound QT prolongation, needs to complete load under observation in hospital with EKG monitoring (however additional information supports quick IV loading).	IKr, β1, β2	IV: 75 mg q12h, PO: 80–120 mg q12h	Prolonged QT	Class III blockage of the delayed potassium rectifier channel leads to longer action potentials and an effective refractory period. In patients with advanced heart failure, Sotalol can cause cardiogenic shock.
Dofetilide	Specific class III antiarrhythmic that inhibits the delayed outward rectifying potassium current, increasing the effective refractory period (ERP) in a reverse use-dependence way but without delaying intracardiac conduction.	IKr	PO only: 500 mcg q12h	Prolonged QT	
Class IV—Calcium Channel Blockers					
Verapamil	Verapamil and diltiazem, non-dihydropyridine calcium channel antagonists, exhibit antiarrhythmic actions primarily at the AV node by inhibiting the slower inward Ca current.	ICa-L	IV: 2.5–5 mg q15–30 mins as tolerated, PO: IR release 120 mg q8h; ER release: 120–480 mg q12h–q24h	Severe EF (<35%) with AV node dysfunction.	Negative inotropy can cause cardiogenic shock. Blocking the inward Ca current extends the effective refractory period (ERP) with minimal impact on atrial/ventricular myocytes or the his-purkinje system.
Diltiazem	Although less common, these agents can cause blockade of slow inward calcium channels on some sensitive fascicular tissues.	ICa-L	IV: 0.25 mg/kg bolus followed by 5–15 mg/h as tolerated, PO: IR release: 30–120 mg q6h–q12h, ER release: 30–240 mg q12h–q24h	Severely Depressed EF (<35%), Severe AV node dysfunction.	Negative inotropy, can precipitate cardiogenic shock.
No Class in Vaughn-Williams					
Ranolazine	Ranolazine works similarly to amiodarone by inhibiting sodium, potassium, and calcium channel depolarisation and repolarisation. The net result is a concentration-dependent extension of action potential duration, which decreases in early depolarisations.	INa, Ikr	PO only: 500–1000 mg q12h	Hepatic Cirrhosis	Can prolong QT

Ivabradine	Ivabradine works at the SA node in a use-dependent manner, blocking the mixed sodium-potassium current (If), reducing pacemaker potential depolarisation and lowering heart rate.	If	PO: 2.5–5 mg q12h	Bradycardia, heart block, sick sinus syndrome.	Symptomatic bradycardia, increase risk of atrial fibrillation.

Table 1: The Pharmacological Characteristics of All Drugs Classified By Vaughan-Williams, Including the Primary Side Effects and Contraindications.

Importance of TDM in Anti-Arrhythmic Drugs

Anti-arrhythmic drugs have a narrow therapeutic index, requiring careful dose titration to avoid toxicity and ensure efficacy.

Safety and Efficacy

Class I Antiarrhythmic Agents: These medications, which inhibit the fast-inward sodium channel, are highly hazardous. TDM improves the safety of these medications Because they block the fast-inward sodium channel, these drugs are extremely hazardous. Through the assurance of appropriate dosage and the reduction of adverse effects, TDM enhances the safety of these drugs.

Procainamide's therapeutic range is 4–10 μg/ml, while quinidine's is 1–5 μg/ml.
TDM is necessary for amiodarone, a class III medication, to keep an eye out for pulmonary toxicity and ensure patient compliance. TDM, however, works less well with sotalol.by assuring proper dose and minimising side effects.

Quinidine and procainamide have therapeutic ranges of 1-5 μg/ml and 4-10 μg/ml respectively [20].
Amiodarone, a class III drug, requires TDM to monitor for pulmonary toxicity and maintain patient adherence. However, TDM is less effective for sotalol.

Other Agents: TDM can significantly improve drugs like digoxin and perhexiline avoid toxicity because their therapeutic ranges coincide with toxic ranges.

Interindividual variability in pharmacokinetics, such as absorption, clearance, and volume of distribution, makes TDM useful for distinguishing between therapeutic failures and inadequate plasma concentrations.

Methods Used in TDM for Anti-Arrhythmic Drugs

Traditional Blood Sampling: Monitoring serum drug concentrations is the standard method for determining optimal doses, but it is costly and time-consuming.

Electrocardiographic (ECG) Monitoring: Changes in ECG parameters, such as the duration of the filtered QRS (f-QRS), can correlate with serum drug concentrations, potentially reducing the need for frequent blood sampling.

Direct Analysis in Real Time-Mass Spectrometry (DART-MS/MS): Multiple antiarrhythmic medications can be quickly and simultaneously quantified in human serum using this approach, giving clinical TDM procedures immediate feedback.

By eliminating the necessity for chromatographic separation, this technique keeps high accuracy and precision while drastically cutting the analysis time to 30 seconds per sample.

We developed a DART-MS/MS approach for the absolute and simultaneous quantitative analysis of metoprolol, diltiazem, amiodarone, propafenone, 5-hydroxy(OH)-propafenone, and verapamil in human serum.

The approach has a short running time (30 s per sample) and achieves great sensitivity with only 2 μL of samples.

During sample preparation, the internal standard with an isotopic label is introduced. The method is validated for linearity, selectivity, accuracy, precision, recoveries, and matrix effect [15,19].

Every day, clinical TDM samples are analyzed with a satisfactory level of accuracy using the DART-MS/MS technique.

The suggested method is helpful in TDM for evaluating toxicity and compliance in patients on anti-arrhythmic drugs.

Additionally, this study shows that DART-MS/MS is a very helpful tool for quantitative and rapid biological matrix analysis without chromatography.

Rapid and Accurate Monitoring

The DART-MS/MS Method: This approach enables the rapid and simultaneous quantification of various anti-arrhythmic medications in human serum, providing useful data for clinical TDM practices.

It eliminates the requirement for chromatographic separation while providing great accuracy and precision [20].

Tool	Efficiency	Limitations	Examples of indications
Clinical history	Always necessary for evaluation of acute and chronic risk profile, symptoms and their evolution	Subjectivity of perception of symptoms and limitations of memory and/or neurological limitations if they exist	All patients
Physical examination	Always necessary for evaluation of acute and chronic risk profile, signs and their evolution	Unable to detect very small/ focal signs	All patients
Electrocardiogram	Always necessary for evaluation of rhythm, heart rate, bundle branch block, PR and QTc intervals and possible presence of arrhythmias or high risk markers (e.g. presence of delta wave). Prognostic value. High availability and low cost	High specificity but low sensitivity for arrhythmias since it evaluates the cardiac electrical activity with high resolution but during a very short period of time	All patients at the initiation and during follow-up
Holter and external loop recorders	High specificity for detection of arrhythmias. Allows prolonged (24 h to 30 days) evaluation of rhythm and heart rate and intervals	Low sensitivity for arrhythmia detection (although higher than with ECG). Higher cost and lower availability than ECG	To evaluate burden of arrhythmia with or w/o AAD
			To evaluate proarrhythmic risk
Implantable loop recorder	High specificity for detection of arrhythmias	The highest sensitivity for arrhythmia detection. Higher cost and lower availability than Holter. Invasive	To evaluate unapparent arrhythmic cause of syncope
Pacemakers and ICDs	High sensitivity and specificity for detection and treatment of arrhythmias	Only available in those patients with already implanted devices	Interrogation for arrhythmia and to evaluate AAD effect on arrhythmia burden
Echocardiogram	Often necessary. Detection of structural heart disease, LVEF and other functional parameters. Non-invasive and without radiation	Constitutional limitations of echocardiographic window may limit the sensitivity. Some availability limitations	Evaluate cardiac substrate of arrhythmias and the effect of arrhythmia on cardiac performance
Transoesophageal echocardiogram	Higher sensitivity than transthoracic echocardiogram for atrial function, morphology and thrombus detection. Without radiation	Invasive. Lower availability than transthoracic echocardiogram	Evaluation of thrombotic risk
Magnetic resonance imaging	Higher sensitivity and specificity for morphological and functional changes than echocardiogram. Includes coronary evaluation.	Time-consuming and expensive equipment. Availability limitations	Evaluation of myocardial scar and atrial fibrosis.
Computed tomography	High sensitivity and specificity for morphological changes and noninvasive coronary angiography. Faster acquisition than MRI	Uses radiation. Expensive equipment Limited availability	Evaluation of coronary circulation (noninvasively) and of myocardial substrate
Exercise testing	Useful for detection of myocardial ischemia, exercise-dependent arrhythmias, evaluation of chronotropism, functional capacity and arterial pressure reaction to exercise.	Sensitivity limitations (especially if left bundle branch block or pacemaker rhythm is present)	Used by many clinicians before administration of class IC AAD

Cardiac nuclear imaging	Similar indications and with higher sensitivity than exercise testing. Useful in presence of advance branch block or pacemakers. Evaluates macro and microcirculation of the heart.	Higher cost than exercise testing. Uses radiation. Limited availability	Evaluation of the ischemia when exercise test results are doubtful or exercise test is not recommended
Coronary angiography	Evaluates the epicardial coronary arteries and their branches. It indicated in selected cases based on clinical context	Invasive. Uses radiation. Risk of contrast induced nephropathy. Limited availability	Evaluation of possible amendable arrhythmia triggers
Electrophysiological study	Useful for precise diagnostic of arrhythmia mechanism and thereapeutical decision-making	Invasive. Uses (usually) radiation. Limited availability	Evaluation of arrhythmia mechanism, especially in the view of future device implantation or ablation

Table 2: The role of diagnostic tools in evaluating patients with arrhythmia for antiarrhythmic drug therapy.

Clinical Features		ECG Changes	
Hypotension	Amiodarone, dronedarone flecainide, ibutilide lidocaine, mexiletine, procainamide, propafenone, quinidine	Wide QRS	Amiodarone, dronedarone, disopyramide, flecainide, procainamide, propafenone quinidine
Heart failure	Disopyramide, flecainide, procainamide, propafenone, sotalol	Prolonged QTc	Amiodarone, dronedarone disopyramide, dofetilide, ibutilide, procainamide, sotalol, quinidine, flecainide, propafenone (only slight prolongation)
Seizures	Flecainide, lidocaine, mexiletine, procainamide, propafenone, quinidine	Ventricular arrythmias	Procainamide
Neurological symptoms and signs	Disopyramide, flecainide, lidocaine, mexiletine, procainamide, propafenone, quinidine	Prolonged PR	Procainamide
Anticholinergic symptoms and signs	Disopyramide, procainamide, quinidine	Torsade de pointes	Ibutilide, dofetilide, sotalol, quinidine, procainamide, disopyramide, amiodarone (rare)
Endocrine changes	Amiodarone (hypo/hyperthyroidism), quinidine, disopyramide (hypoglycemia)	Increased ventricular rate in atrial flutter	Quinidine, flecainide, propafenone
Pulmonary changes	Amiodarone (fibrosis, pneumonitis)		
Hematological/oncological changes	Amiodarone (hepatobiliary carcinoma), procainamide (hemorrhagic syndromes)		
Autoimmune manifestations	Procainamide (lupus-like syndrome, vasculitis)	Incessant ventricular tachycardia	Flecainide, propafenone, quinidine (rare)
Skin changes	Procainamide, propafenone		

Figure 6: Clinical features and ECG changes.

Drug	F (%)	Protein binding (%)	Vd (L/kg)	Metabolism	Half-life (hours)	Elimination (H/R, %)	$C_{max\ (mg/ml)}$	Active-metabolites
Adenosine (IV)					10-30 s			
Amiodarone (PO, IV)	35-65	99	66	CYP3A4 and 2C8	58 days	99/1	1-2.5	Desethylamiodarone
Bisoprolol	90	30	3.5	CYP3A4	10-Dec	50/50		

Esmolol (IV)	-			Hydrolysis	9 min			
Digoxin (PO, IV)	60-75	25	3.5	No CYP450	35	20/80	0.5-1	
Diltiazem (PO, IV)	38	80	3.3	CYP3A4	3.5-5	65/35 (1-3*)	0.1-0.2	Deacetyldiltiazem
Disopyramide (IV)	60-85	50-65	0.6	CYP3A4	06-Sep	45/55	02-May	Mono-N-dealkylated
Dofetilide	95	65	3.4	CYP3A4	Jul-13	20/80	2.3**	N-debutyl metabolite
Dronedarone	5	>98	20	CYP3A4	13-19	84		
Ibutilide (IV)	-	40	11	No	2-12 (6)	18/82 (7*)	-	a-OH-ibutilide
Flecainide	95	40-50	5.5-10	CYP2D6	20(12-27)	10/85 (35*)	0.2-1	Meta-O-dealkylflecainide
Lidocaine	30	70	1.1	CYP1A2 (3A4)	1.5-2	90/<10*	1.5-5	GX, MEGX
Metoprolol tartrate	40-50	12	3.5	CYP2D6	3-5 (2.8 EM; 7.5 PM)	(<5**)		
Mexiletine	85-90	50-70	05-Jun	CYP2D6 and 1A2	Oct-20	90/10*	0.5-2	N-methylmexiletine
Nadolol	30	30		Not metabolized	20-24	-/95		
Procainamide	85	15-20	2	Hydrolysis	03-May	40/60	03-Aug	N-acetyl-procainamide
Propafenone	May-30	95	2.5-4	CYP2D6 (3A4, 1A2)	2-10 EM; 10-32 PM	95/5 (1*)	0.2-3	5-OH-propafenone
Propranolol	25-35	90	2	CYP2D6 (1A2)	02-Jun	99/1	10-100**	4-OH-propranolol
Quinidine	70-80	80-90	2.7	CYP3A4	06-Aug	80/20*	02-Jun	3-OH-quinidine
Sotalol	90-100	0	1.5-2.5	Not metabolized	12 (7-18)	15/85*	<5	
Verapamil (PO, IV)	20-30	90	5	CYP3A4	2-7.5[a]	15/80 (<5*)	0.1-0.3	Norverapamil
Vernakalant (IV)		40-55	2.3	CYP2D6	3-5.5	85/14	03-Aug	

Table 3: Pharmacokinetic characteristics of antiarrhythmic drugs.

Pharmacogenetic Considerations:

Pharmacogenetics is the study of the genetic variations that underlie different drug reactions. Inter-individual heterogeneity in the response to AAD medications is influenced by two main categories of genetic variants. The processes of absorption, distribution, metabolism, and elimination influence the concentration of drug (and active metabolites) at the target location, hence determining pharmacokinetic variability. The PK variability in AAD effects can be explained by variations in the genes that produce certain transporters and metabolizing enzymes, especially those in the CYP450 superfamily. This variability has less of an effect on AAD metabolized or removed via many pathways, but it is important for AAD with a single dominant route of metabolism or elimination (digoxin, dofetilide, propafenone, and sotalol). AADs are mostly metabolized by the enzymes CYP2D6, CYP2C9, and CYP3A4-5 [11,13].

Although the antiarrhythmic efficacy of the medicine is not well established, poor metabolizers have greater drug plasma levels and a higher chance of side effects. AAD plasma levels are also significantly raised or decreased by

CYP450 inducers and inhibitors. For instance, NAPA, a Class III AAD that lengthens the QT interval, is produced by the metabolism of procainamide. Slow acetylators are more likely to develop drug-induced lupus and had greater plasma levels of procainamide. Digoxin toxicity and plasma levels are increased by Pgp inhibitors, and P-glycoprotein serves as an efflux pump. The complex biological environment in which the drug-target interaction takes place, as well as differences in the target molecules (channels, receptors, and transporters) that AAD interacts with to produce positive or negative effects, are the main causes of pharmacodynamic variability. Blood pressure and heart rate reactions to β-blockers and agonists are influenced by variations in the genes encoding beta-adrenoceptors. The main problem with AAD therapy is proarrhythmia, which can happen even in the absence of clear risk factors. Polymorphisms in genes that produce cardiac ion channel components have been linked to an increased risk of torsades de pointes following QT-prolonging medication, and several AADs block cardiac ion channels. The complex biological environment in which the drug-target interaction takes place, as well as differences in the target molecules (channels, receptors, and transporters) that AAD interacts with to produce positive or negative effects, are the main causes of pharmacodynamic variability. Blood pressure and heart rate reactions to β-blockers and agonists are influenced by variations in the genes encoding beta-adrenoceptors. The main problem with AAD therapy is proarrhythmia, which can happen even in the absence of clear risk factors. Polymorphisms in genes that produce cardiac ion channel components have been linked to an increased risk of torsades de pointes following QT-prolonging medication, and several AADs block cardiac ion channels. Indeed, uncommon mutations in genes that cause congenital arrhythmia syndromes are common in patients with drug-induced LQTS. Proarrhythmia is typically associated with drug exposure, hence both genetic and pharmacological changes in CYP450 activity are risk factors for drug-induced proarrhythmia. Even when existing genetic data indicate a clear opportunity to improve the management of cardiac arrhythmias, the extent to which PK/PD genetic variations are associated with clinical outcomes is unidentified, and their predictive value in determining AAD efficacy and safety is not established [21,22].

Flecainide: Flecainide clearance is impacted by the CYP2D6 genotype, especially in elderly individuals. TDM can be guided by pharmacogenetic information to successfully modify dosages and prevent side effects.

Genes affecting the response	Product	Substrates*	Potential effect
Pharmacokinetic			
MDR1	P-gp drug transporter*	Digoxin, diltiazem, phenytoin, propranolol, quinidine, verapamil	Variants (MDR1 C3435T) and P-gp inhibitors (amiodarone, diltiazem, dronedarone, quinidine, verapamil): increase digoxin plasma levels and toxicity
SLC22A2	Renal tubular cationic transport (OCT2)	Dofetilide	Inhibitors increase dofetilide plasma levels and prolong the QT interval
CYP3A4/5	Drug-metabolizing enzymes*	Amiodarone, diltiazem, disopyramide, dofetilide, dronedarone, mexiletine, propafenone, quinidine, verapamil	CYP activity can be induced/inhibited by multiple drugs*
CYP2D6		Beta-blockers (atenolol, carvedilol, metoprolol, propranolol, timolol), flecainide, mexiletine, propafenone, quinidine, vernakalant	Poor metabolisers: higher plasma concentrations and higher risk of adverse effects.
			Propafenone produces more heart rate slowing and neurotoxicity
			Lower levels of active metabolites (propafenone, quinidine)
			Ultra-rapid metabolizers: decreased drug efficacy
NAT2		Procainamide	Slow acetylators: higher risk of drug-induced lupus syndrome.
PHARMACODYNAMIC:			

KCNH2/KCNE2	I_{Kr}	Modulate the risk of ventricular arrhythmias and TdP in patients treated with QT-prolonging drugs	Sublinical congenital long QT syndrome variants (SCN5A S1103Y, KCNE1 D85N, KCNE2 T8A) predispose to TdP
KCNQ1/KCNE1	I_{Ks}		Increased TdP risk in patients treated with Class IA, IC and III AAD and other QT-prolonging drugs
SCN5A	I_{Na}		Class IA and C AAD unmask
NOS1AP	Nitric oxide synthase 1 adaptor protein		Concealed Brugada syndrome phenotype can be unmasked by class IA and IC AAD
ADBR1, ADRB2	b1/b2-adrenoceptors	Beta-blockers/agonists	Modulate drug responses on heart rate and blood pressure in patients with hypertension and HF
GRK5	GRK5	G protein-coupled receptor kinase 5	
RYR2, CASQ2, CaMKII	Ca^{2+} handling proteins	Digoxin	Loss-of-function variants predisposes to digitalis-induced arrhythmias
ANK2	Membrane associated adaptor		

Table 4: Genetic variants implicated in pharmacokinetic and pharmacodynamic variability in anti-arrhythmic drug efficacy and safety.

Conclusion

The safe and efficient use of anti-arrhythmic medications depends on TDM. Optimizing anti-arrhythmic medication is aided by developments in analytical techniques, knowledge of therapeutic ranges, pharmacogenetic insights, and awareness of drug interactions. The study and clinical application of several medications used to treat cardiac rhythm abnormalities have greatly benefited by therapeutic drug monitoring. This is particularly true for digoxin and perhexiline, which are Class I agents. TDM offers certain benefits in monitoring amiodarone toxicity and compliance, but it is less successful in monitoring the use of β-adrenoceptor blockers and Class IV drugs. Pharmacogenetic considerations, such as the CYP2D6 genotype and genetic variations in the cardiac sodium channel gene and β1-adrenergic receptor, can influence the efficacy and therapeutic range of anti-arrhythmic drugs. Therapeutic drug monitoring (TDM) is crucial for the development and clinical application of Class I agents, perhexiline, and digoxin, but less important for β-adrenoceptor blockers and Class IV drugs. TDM may become less relevant as the number of Class I antiarrhythmic drugs declines worldwide, but it might still be necessary for newly developed Class III agents. Their limited therapeutic window raises concerns about drug interactions, which might result in side effects such cardiac failure and recurrent arrhythmias. TDM improves the safety and effectiveness of anti-arrhythmic medications in clinical practice by customizing treatment to meet the needs of each patient. The accuracy and efficacy of TDM in clinical practice are further improved by the use of pharmacogenetic data and sophisticated quantification techniques.

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