Class 1: Sodium Channel Blockers—Antiarrhythmic Drugs

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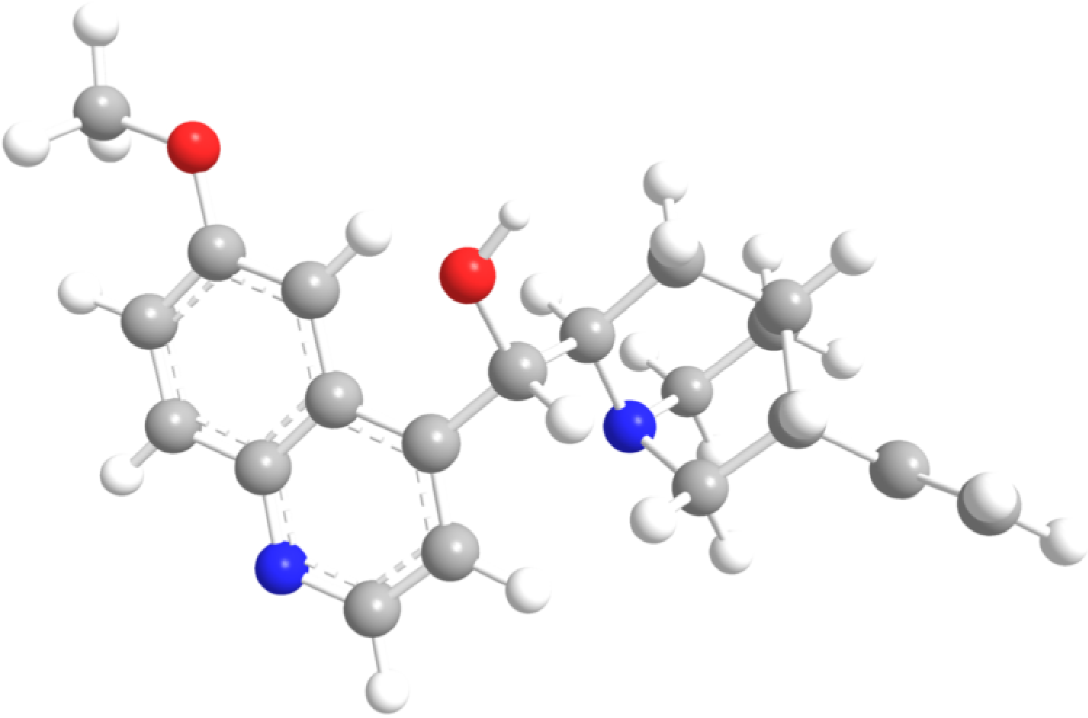
The Vaughan-Williams classification is one of the most commonly used classifications for antiarrhythmic drugs. Class 1 consists of sodium channel blockers, which in turn is divided into 3 subgroups namely 1-A, 1-B, and 1-C. This article discusses the class 1 antiarrhythmic drugs in detail, along with a description of the salient features of the individual drugs.



Antiarrhythmic Drugs

The Vaughan-Williams classification is one of the most commonly used classifications for antiarrhythmic drugs. It is very important to classify a drug so that its possible benefits can be explored. This classification groups the drugs based on their general effect (based on the mechanism of action). The drugs are grouped into five classes.

Note: This is a very common USMLE topic.

Class 1 consists of sodium channel blockers, which are in turn divided into three subgroups—classes 1-A, 1-B, and 1-C. This will be explained in detail in the Mechanism of Action section.

Class 2 consists of beta blockers, which basically reduce the heart rate and conduction and cause a reduction of sympathetic activity.

Class 3 consists of potassium channel blockers; these work by prolonging the repolarization phase, thereby increasing the duration of the action potential. This essentially culminates in increasing the effective refractory period.

Class 4 consists of calcium channel blockers; these work by blocking the L-type calcium channels. These channels are normally found along the conduction pathway, especially near the sinoatrial (SA) node and the atrioventricular (AV) node. By blocking these channels, these drugs reduce the heart rate and the speed of conduction in the heart.

Class 5 antiarrhythmic drugs are agents that cannot be categorized into the above groups.

This article discusses the class 1 antiarrhythmic drugs in detail, along with a description of the salient features of individual drugs.

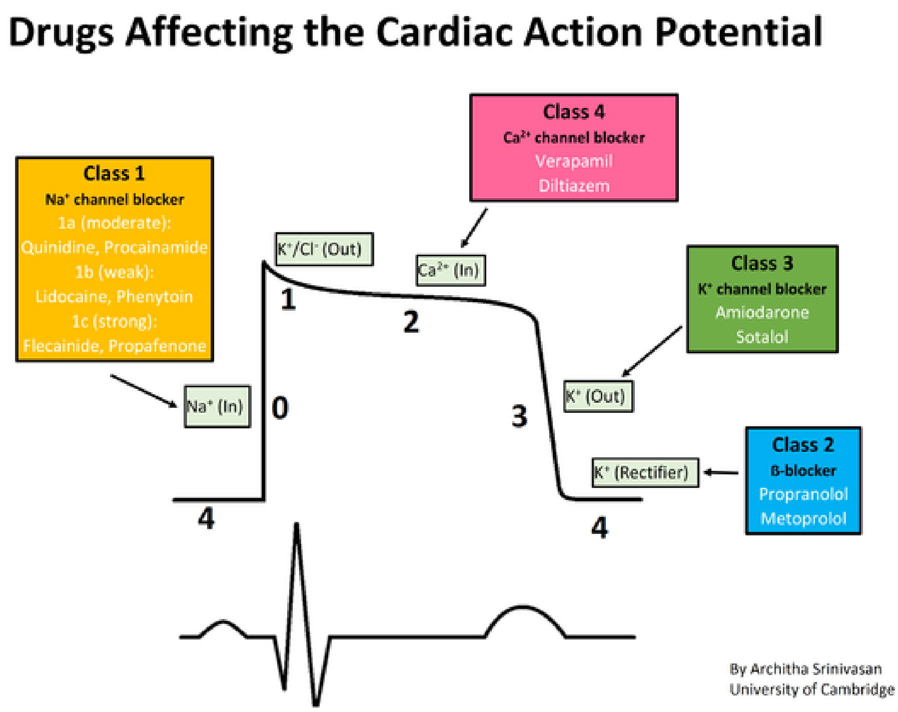
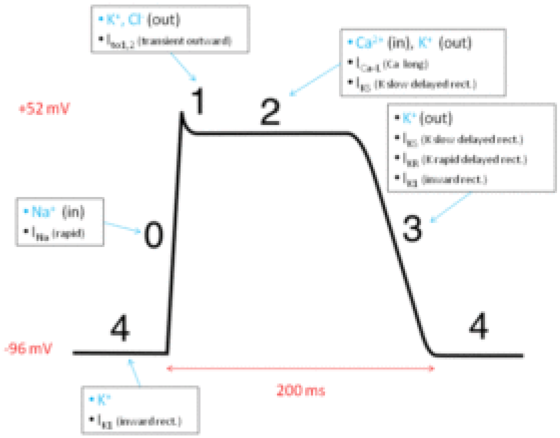


Image : Drugs affecting the cardiac action potential. By Architha Srinivasan. License: CC BY-SA 4.0.

The action potential



[Image](): Basic cardiac action potential. By Action_potential2.svg: *Action_potential.png: User:Quasar derivative work: Mnokel (talk) derivative work: Silvia3 (talk) – Action_potential2.svg. License: CC BY-SA 3.0.

The trajectory followed by the action potential will depend on the membrane potential of the cardiac cells, which varies between different parts of the heart. **There is a normal rise followed by a fall in the action potential.**

Phase 0 represents the rapid depolarization phase that occurs because of the influx of sodium. Phases 2 and 3 represent the repolarization phase. In both of these cases, there is the prominent efflux of potassium in addition to other ions. In Phase 2, the potential, arising through the efflux of potassium, is balanced by the influx of calcium, thus causing the action potential to remain as a horizontal line.

Mechanism of Action of Sodium Channel Blockers

Sodium channel blockers comprise the class 1 antiarrhythmic compounds according to the Vaughan–Williams classification scheme. These drugs bind to and block the fast sodium channels that are responsible for the rapid depolarization (phase 0) of fast-response cardiac action potentials. This type of action potential is found in non-nodal cardiomyocytes (e.g., atrial and ventricular myocytes and Purkinje tissue).

Because the slope of phase 0 depends on the activation of fast sodium channels and the rapid entry of sodium ions into the cell, blocking these channels decreases the slope of phase 0, which also leads to a decrease in the amplitude of the action potential. In contrast, nodal tissue action potentials (in the SA node and the AV node) do not depend on fast sodium channels for depolarization; instead, phase 0 depolarization is carried out by calcium currents. Therefore, sodium channel blockers have no direct effect on nodal tissue, at least through the blockade of fast sodium channels.

Therefore, blocking sodium channels reduces the velocity of action potential transmission within the heart (reduced conduction velocity; negative dromotropy). This can serve as an important mechanism for suppressing tachycardias that are caused by abnormal conduction (e.g., re-entry mechanisms). By decreasing abnormal conduction, re-entry mechanisms can be interrupted.

The differences between the three subgroups within class 1 are that, in addition to affecting phase 0 of the action potentials, sodium channel blockers may also alter the action potential duration (APD) and effective refractory period (ERP). Because some sodium channel blockers increase the ERP (class 1-A), while others decrease it (class 1-B) or have no effect on it (class 1-C), the Vaughan–Williams classification recognizes these differences as subclasses of class 1 antiarrhythmic drugs.

Effects on repolarization

The effects on ERP are not directly related to the sodium channel blockade but instead are related to drug actions on potassium channels involved in phase 3 repolarization of action potentials. These channels regulate potassium efflux from the cell (K+ out), and therefore affect repolarization. The drugs in these subclasses also differ in their efficacy for reducing the slope of phase 0, with class 1-C drugs having the greatest and class 1-B drugs having the smallest effect on phase 0 (class 1-A drugs are intermediate in their effect on phase 0).

The following summarizes these differences:

Sodium channel blockade:
class 1-C > class 1-A > class 1-B

Increasing ERP:
class 1-A > class 1-C > class 1-B (decreases)

Increasing or decreasing the APD and ERP can either increase or decrease arrhythmogenesis, depending on the underlying cause of the arrhythmia. Increasing the ERP, for example, can interrupt tachycardia caused by re-entry mechanisms (class 1-A) by prolonging the duration that normal tissue is unexcitable (its refractory period).

This can prevent re-entry currents from reexciting the tissue, as happens with Wolff–Parkinson–White syndrome (WPW), which is caused by an aberrant pathway. On the other hand, increasing the APD can precipitate torsades de pointes, a type of ventricular tachycardia caused by afterdepolarizations (abnormal depolarizations of cardiac myocytes that interrupt phase 2, phase 3, or phase 4 of the cardiac action potential in the electrical conduction system of the heart).

Effects on automaticity

Class 1 antiarrhythmic agents can suppress abnormal automaticity by decreasing the slope of phase 4, which is generated by pacemaker currents. The mechanism for this is not understood and is unrelated to blocking fast sodium channels.

Indirect vagal effects

The anticholinergic effect seen with this group of drugs increases the conduction along the SA and AV pathways. Thus, in a patient with atrial flutter, although the ventricular rate will be reduced by their sodium blocking property, class 1 antiarrhythmics can lead to an increase in both the SA rate and the AV conduction, which can offset the direct effects of the drugs on these tissues.

Although a class 1-A drug may effectively decrease the atrial rate during flutter, it can lead to an increase in ventricular rate because of an increase in the number of impulses conducted through the AV node (anticholinergic effect), thereby requiring concomitant treatment with a beta blocker or calcium channel blocker to slow the AV nodal conduction. These anticholinergic actions are most prominent at the SA and AV nodes because they are extensively innervated by vagal afferent nerves. Different drugs within the class 1-A subclassification differ in their anticholinergic actions.

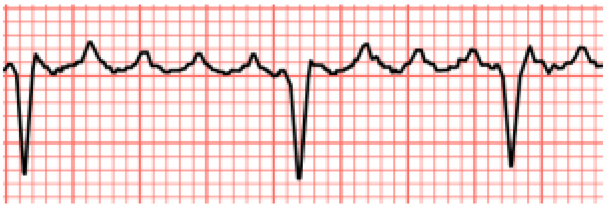


Image: Atrial flutter with variable block (between 3 and 4 to 1). By James Heilman, MD. License: CC BY-SA 3.0.

Pros and Cons and Main Indications for the Use of Sodium Channel Blockers

All three classes of drugs are indicated for the treatment of ventricular tachyarrhythmias.

In addition, class 1-C drugs are very valuable in the life-threatening supraventricular tachyarrhythmias (flecainide and propafenone). Class 1-A drugs also have an effect on atrial fibrillation, along with flutter and supraventricular tachycardia.

Adverse and Side Effects Related to the Use of Sodium Channel Blockers

The side effects are discussed in detail for individual drugs.

The increase or decrease in action potential duration and the effective refractory period can act as a double-edged sword. Both of these mechanisms prevent the re-entry circuits, but, at the same time, they increase the potential for causing torsades de pointes. The proarrhythmogenic potential is generally seen in this group of drugs.

Disopyramide

Indications

In addition to the indications discussed above, important consideration needs to be given to those patients who have uncontrolled atrial fibrillation. The administration of disopyramide will cause an increase in the AV nodal conduction, thereby increasing the ventricular rate in these patients.

This effect also occurs with procainamide and quinidine. Treatment with beta blockers, digoxin, or a calcium channel blocker is required. Disopyramide is deemed safe in patients with hypertrophic cardiomyopathy and is shown to have beneficial effects.

Side effects

Disopyramide has significant cardiac toxicity: It **decreases the contraction of the heart (negative inotropic effect) and has the potential to cause arrhythmia**. The decrease is seen even with a dose as low as 1 mg/kg and may precipitate heart failure or aggravate it in patients with pre-existing heart failure.

A common side effect of disopyramide is related to its anticholinergic effects. This includes dryness of the mouth, hesitancy during urination, and constipation.

In conditions in which cholinergic activity is already decreased (such as in myasthenia gravis, in which antibodies against acetylcholine receptors are formed), the administration of this drug will aggravate the condition.

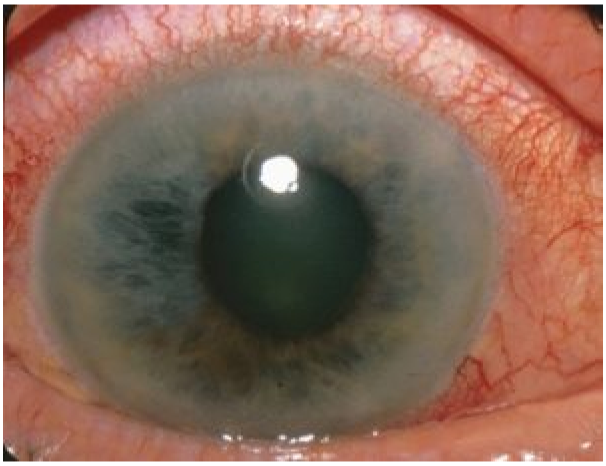


Image: Photograph showing acute angle closure glaucoma, which is a sudden elevation in intraocular pressure that occurs when the iris blocks the eye's drainage channel—the trabecular meshwork. By Jonathan Trobe, MD—The Eyes Have It. License: CC BY 3.0.

The other conditions in which caution needs to be exercised are acute angle closure glaucoma and urinary retention. It causes **widening of the QRS complex and prolongation of the QT interval**. Although it is rare, hypoglycemia may occur with disopyramide therapy because disopyramide may induce inhibition of the K–ATP channels.

Monitoring available for prevention of side effects

In order to prevent the anticholinergic effect, the monitoring of serum concentrations of mono-N-dialkyl disopyramide is required in renally deranged patients.

Treatment of side effects

Although a decrease in contractility with disopyramide is self-limiting, short-term treatment with diuretics and an inotropic agent might be required.

The anticholinergic effect can be counteracted by administering physostigmine and pyridostigmine, both of which increase the cholinergic activity.

QRS complex widening and prolongation of the QT interval require discontinuation of treatment with disopyramide. In patients who require treatment for prolongation of QT interval, intravenous magnesium sulfate may be required to stabilize the depolarization.

Procainamide

Side effects of procainamide

One of the most important known side effects of procainamide is its potential to cause a lupus-like syndrome, which is especially common with long-term administration of the drug. The blood of these patients will have a positive antinuclear antibody titer (meaning that the antibodies are essentially formed against the patient's own nuclear elements).

Image: Back and front of a hand of a person with Raynaud's disease. By Vertebro. License: Public domain.

The other side effects include loss of appetite, the sensation of vomiting, headache, loss of sleep, dizziness, hallucination, psychosis (rare but reported), rashes that are characteristically morbilliform in nature, conditions affecting the blood vessels (such as Raynaud's phenomenon), and vasculitis of the digital ends.

Similar to disopyramide, administration of procainamide results in a potential for prolongation of the QRS complex and the QT interval and the occurrence of ventricular arrhythmia.

The drug also increases the risk of arrhythmias and is an arrhythmogenic agent. The most common arrhythmia caused by procainamide is a form of polymorphic ventricular tachycardia known as 'torsades de pointes.'

Bone marrow suppression is one of the dreaded side effects of procainamide; the possibility of this side effect leads to patients objecting to the routine use of this drug.

Pancytopenia and agranulocytosis occur in this condition. Their causes are not well delineated and might range from allergic to hypersensitivity reactions.

Treatment of side effects

The symptoms of a lupus-like syndrome occur in a very few patients, and even in those patients, it is self-limiting after the treatment is stopped. Other alterations include considering alternatives like N-acetyl procainamide, which does not have the potential to cause lupus.

The occurrence of bone marrow suppression warrants immediate discontinuation of the drug.

Quinidine

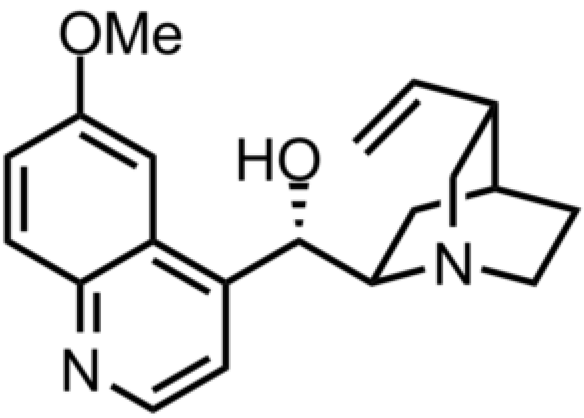


Image: Chemical structure of quinidine. By Ymwang42 — Using ChemDraq11.0. License: CC0.

Quinidine can be used for the treatment of both ventricular and atrial arrhythmias.

Special indication for quinidine

Brugada syndrome is a genetic disorder associated with the development of ventricular arrhythmias.

Patients with this syndrome are characterized by the potential for sudden cardiac death. Implantation of a cardioverter–defibrillator (ICD) is the gold standard for prevention.

Quinidine has shown promise in patients with this syndrome and is a standard alternative treatment. A recent study proclaims this effect; the study included 96 patients with a mean follow-up of 113 months.

In a systematic review in which the various antiarrhythmic drugs were evaluated for atrial fibrillation, although quinidine reduced the recurrence of atrial fibrillation, it was associated with increased mortality and was the most proarrhythmogenic agent among the tested classes of drugs (classes 1-A, 1-C, and 3).

Side effects of quinidine

As with other drugs in the class A group, quinidine is also proarrhythmogenic and has the potential to cause sudden death, thus reducing the frequency of its routine use. Like disopyramide, it can also precipitate heart failure.

Bigeminy and premature ventricular tachycardia are characteristic arrhythmias caused by quinidine. Prolongation of the QT interval (related to a delay in repolarization), which causes the risk of torsades de pointes, is caused by this drug (maximally).

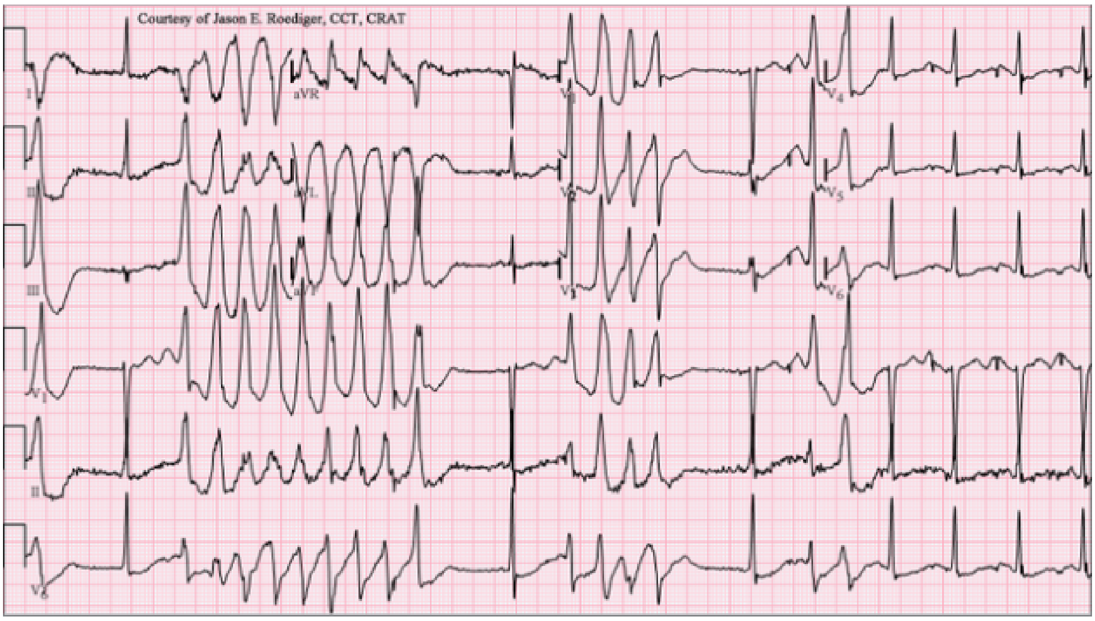


Image: Prolonged QT interval: torsades de pointes (TdP). By Jer5150 – Own work. License: CC BY-SA 3.0.

The risk of digitalis toxicity is enhanced with quinidine administration. Other risk factors include the presence of hypokalemia. The risk of hypotension is exacerbated by the rapid administration of a very large dose of quinidine. The reason is the direct vasodilatory property of quinidine. Quinidine is also associated with a hypoglycemic effect and immune-mediated reactions.

Quinidine toxicity is described by the characteristic term ‘cinchonism.’ The signs and symptoms of cinchonism include blurring of vision, ringing in the ears (known as tinnitus), psychosis, confusion, delirium, and headache.

Treatment of side effects

Torsades de pointes can be treated by artificially increasing the pace of circulation through the atria and the ventricles and by the intravenous administration of isoproterenol.

One method to prevent torsades de points is alkalization with sodium bicarbonate (basically, the alkalosis enhances the recovery of sodium channels). The intravenous administration of magnesium sulfate, as discussed for disopyramide, is another alternative.

Lidocaine and Its Analogs

Indications

Lidocaine is available only in intravenous form and is indicated for ventricular tachycardia. Disopyramide and mexiletine are orally active lidocaine analogs. Patients who have myocardial ischemia in addition to arrhythmias will benefit from the administration of lidocaine and mexiletine, because these drugs have improved efficacy against the ischemic myocardium.

Side effects

Image: A chest radiograph of a patient with idiopathic pulmonary fibrosis (IPF). By IPFeditor – Own work. License: CC BY-SA 3.0.

Tocainide has the potential to cause pulmonary fibrosis in the lungs.

Class 1-C Drugs

Propafenone and flecainide: In contrast to the protective effect seen with the class 1-B drugs in patients with myocardial infarction, class 1-C compounds carry an increased risk of death in patients with myocardial infarction (the CAST trial).

Propafenone, in addition to its sodium blocking property, also has beta blocking and calcium channel blocking activity. Both of these cause a decrease in conduction and can precipitate or aggravate heart failure.

Flecainide has the potential to induce life-threatening ventricular tachycardia.

References

Sherrid, M.V., Barac, I., McKenna, W.J., Elliott, P.M., Dickie, S., Chojnowska, L., et al. (2005). Multicenter study of the efficacy and safety of disopyramide in obstructive hypertrophic cardiomyopathy. *Journal of the American College of Cardiology*, 45(8):1251–8. PubMed PMID: 15837258. Epub 2005/04/20.

Di Bianco R, Gottdiener JS, Singh SN, Fletcher RD. A Review of the Effects of Disopyramide Phosphate on the Left Ventricular Function and the Peripheral Circulation. Angiology. 1987 Feb;38(2 Pt 2):174-83. PubMed PMID: 3103491. Epub 1987/02/01. eng.

Negishi M, Shimomura K, Proks P, Mori M, Shimomura Y. Mechanism of Disopyramide-Induced Hypoglycaemia in a Patient with Type 2 Diabetes. Diabetic Medicine. 2009 Jan;26(1):76-8. PubMed PMID: 19125764. Epub 2009/01/08. eng.

Tzivoni D, Banai S, Schuger C, Benhorin J, Keren A, Gottlieb S, et al. Treatment of Torsade de Pointes with Magnesium Sulfate. Circulation. 1988 Feb;77(2):392-7. PubMed PMID: 3338130. Epub 1988/02/01. eng.

Belhassen B, Rahkovich M, Michowitz Y, Glick A, Viskin S. Management of Brugada Syndrome: Thirty-Three-Year Experience Using Electrophysiologically Guided Therapy With Class 1A Antiarrhythmic Drugs. Circulation Arrhythmia and Electrophysiology. 2015 Dec;8(6):1393-402. PubMed PMID: 26354972. Epub 2015/09/12. eng.

Lafuente-Lafuente C, Mouly S, Longas-Tejero MA, Mahe I, Bergmann JF. Antiarrhythmic Drugs for Maintaining Sinus Rhythm after Cardioversion of Atrial Fibrillation: A Systematic Review of Randomized Controlled Trials. Archives of Internal Medicine. 2006 Apr 10;166(7):719-28. PubMed PMID: 16606807. Epub 2006/04/12. eng.

Roden DM, Woosley RL, Primm RK. Incidence and Clinical Features of the Quinidine-Associated Long QT Syndrome: Implications for Patient Care. American Heart Journal. 1986 Jun;111(6):1088-93. PubMed PMID: 3716982. Epub 1986/06/01. eng.

Echt DS, Liebson PR, Mitchell LB, Peters RW, Obias-Manno D, Barker AH, et al. Mortality and Morbidity in Patients Receiving Encainide, Flecainide, or a Placebo. The Cardiac Arrhythmia Suppression Trial. New England Journal of Medicine. 1991 Mar 21;324(12):781-8. PubMed PMID: 1900101. Epub 1991/03/21. eng.

Notes