ISSN: 0975-766X
CODEN: IJPTFI
Available Online through *Review Article*
www.ijptonline.com

REVIEW ARTICLE OF DISOPYRAMIDE PHOSPHATE DRUG

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Received on 20-06-2018 *Accepted on: 18-08-2018*

Abstract

Antiarrhythmic drugs are drugs used to prevent or treat irregularities of cardiac rhythm. Ischaemia, electrolyte and pH imbalance, mechanical injury, stretching, neurogenic and drug influences, including antiarrhythmics themselves, can cause arrhythmias by altering electrophysiological properties of cardiac fibres. From American Heart Association original research article related to Safety of Outpatient Initiation of Disopyramide for Obstructive Hypertrophic Cardiomyopathy Patients that Disopyramide is effective in ameliorating symptoms in patients with hypertrophic cardiomyopathy; however, its potential for proarrhythmic effect has raised concerns about its use in the ambulatory setting. The risk of initiating disopyramide in this manner has never been evaluated. Disopyramide Phosphate is an effective antiarrhythmic agent, especially for the management of ventricular arrhythmias. It is a Class IA membrane stabilizing agents (Na^+ channel blockers), moderately decrease dv/dt of 0 phase. Initiation of disopyramide in the outpatient setting is safe and the risk of subsequent sudden cardiac death is low. Because of its QT-prolonging effect, precautions may be necessary in patients

Keywords: Disopyramide phosphate, Antiarrhythmic drugs, Cardiac rhythm, Myocardial Infarction (MI), Atrial Flutter (AFI), Atrial Fibrillation (AF)

Introduction:

Antiarrhythmic drugs are drugs used to prevent or treat irregularities of cardiac rhythm. Ischaemia, electrolyte and pH imbalance, mechanical injury, stretching, neurogenic and drug influences, including antiarrhythmics themselves, can cause arrhythmias by altering electrophysiological properties of cardiac fibres. Antiarrhythmic drugs act by blocking myocardial Na^+, K^+ or Ca^{2+} channel. Some have additional or even primary autonomic effects. Classification of antiarrhythmic drugs has been unsatisfactory, because many drugs have more than one action. Vaughan Williams (1969) proposed a 4 Class system which takes into account the most important property

of a drug which is apparently responsible for its antiarrhythmic action in the clinical setting. This system, though arbitrary, is widely accepted. Class I: The primary action of drugs in this class is to limit the conductance of Na^+ (and K^+) across cell membrane-a local anaesthetic action. They also reduce of phase-4 depolarization in automatic cells. The subclass IA containing the oldest antiarrhythmic drugs quinidine and procainamide are open state Na^+ channel blockers which also moderately delay channel recovery (1-10s), suppress A-V conduction and prolong refractoriness. The Na^+ channel blockage is greater at higher frequency (premature depolarization is affected more). These actions serve to extinguish ectopic pacemakers that are often responsible for triggered arrhythmias and abolish re-entry by converting unidirectional block into bidirectional block.

Disopyramide:

It is an effective antiarrhythmic agent, especially for the management of ventricular arrhythmias. It is a Class IA membrane stabilizing agents (Na^+ channel blockers), moderately decrease dv/dt of 0 phase.

Physical Characteristics of Disopyramide Phosphate:

This compound belongs to the class of organic compounds known as pheniramines. These are compounds containing a pheniramine moiety, which is structurally characterized by the presence of a 2-benzylpyridine linked to an dimethyl (propyl)amine to form a dimethyl[3-phenyl-3-(pyridin-2-yl)propyl]amine skeleton.

Physical Properties:

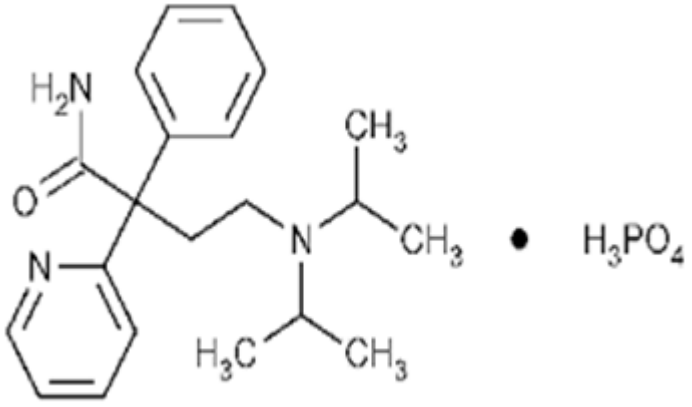
Molecular weight	437.47
Appearance	White Solid
Melting point range	94.5-65^{o}C
pH	Between 4.0 and 5.0 in a solution
Bioavailability	80%
Protein Binding	50%-60%
Half life	6.7 hours
Metabolism	Hepatic, It is partly metabolized in the liver by dealkylation
Route of elimination	In healthy men, about 50% of a given dose of disopyramide is excreted in the urine as the unchanged drug, about 20% as the mono-N-dealkylated metabolite and 10% as the other metabolites.
Loss on drying	Dry it at 105^o for 4 hours, it loses not more than

	0.5% of its weight
Heavy metals	0.002%
Solubility	Water solubilty 44.9 mg/L, methanol, glacial acetic acid, etc
Log P	2.58
pKa	Strongest acid- 16.19 and strongest basic – 10.42
Identification	Infrared Absorption, a solution (1 in 200) responds to the tests for Phosphate
Assay	Dissolved about 160mg of Disopyramide Phosphate, accurately weighed, in 50 mL of glacial acetic acid TS, and titrate with 0.1 N perchloric acid VS, determining the endpoint potentiometrically. Perform a blank determination, and make any necessary correction. Each mL of 0.1 N perchloric acid is equivalent to 21.87 mg of $C_{21}H_{29}N_3O.\ H_3PO_4$
Packaging and storage	Preserve in tight, light- resistand containers

Chemical Properties

Molecular Formula: $C_{21}H_{29}N_3O.\ H_3PO_4$

Chemical name: 4-[bis(propan-2-yl)amino]-2-phenyl-2-(pyridin-2-yl)butanamide; phosphoric acid



Structure: Disopyramide

Chromatographic purity:

Standard solution: Prepare solution A and B of USP Disopyramide Phosphate RS in methanol having concentration of about 50 and 100 µg per mL, respectively.

Test solution: prepare a solution of Disopyramide phosphate in methanol having a concentration of about 10 mg per mL.

Procedure: Separately apply 10- µL portion of the Standard solution A and B and the test solution to a suitable thin-layer chromatographic plate, coated with a 0.25-mm layer of chromatographic silica gel. Allow the spots to dry, and develop the chromatogram in a solvent system consisting of a mixture of toluene, dehydrated alocohol and ammonium hydroxide (170:28:2) until the solvent front has moved about three-fourths of the length of the plate. Remove the plate from the chamber, allow to air-dry, and spray with Potassium Bismuth iodide TS: the R_F value of the principal spot obtained from the Test solution corresponds to that obtained from Standard solution B. Estimate the levels of any additional spots observed in the chromatogram of the Test preparation by comparison with the principal spots in the chromatograms of Standard solution A and B; the sum of the intensities of any additional spots observed is not greater than that obtained from Standard solution B (equivalent to 1%).

Disopyramide Phoshate contains not less than 98.0 percent and not more than 102.2 percent of $C_{21}H_{29}N_3O.\ H_3PO_4$, calculated on the dried basis.

Pharmacodynamics:

Disopyramide is an antiarrhythmic drug indicated for the treatment of documented ventricular arrhythmias, such as sustained ventricular tachycardia that are life-threatening. In man, Disopyramide at therapeutic plasma levels shortens the sinus node recovery time, lengthens the effective refractory period of the atrium, and has a minimal effect on the effective refractory period of the AV node. Little effect has been shown on AV-nodal and His-Purkinje conduction times or QRS duration. However, prolongation of conduction in accessory pathways occurs.

Mechanism of action:

Disopyramide is a Type 1A antiarrhythmic drug (ie, similar to procainamide and quinidine). It inhibits the fast sodium channels. In animal studies Disopyramide decreases the rate of diastolic depolarization (phase 4) in cells with augmented automaticity, decreases the upstroke velocity (phase 0) and increases the action potential duration of normal cardiac cells, decreases the disparity in refractoriness between infarcted and adjacent normally perfused myocardium, and has no effect on alpha- or beta-adrenergic receptors.

Indication:

For the treatment of documented ventricular arrhythmias, such as sustained ventricular tachycardia, ventricular pre-excitation and cardiac dysrhythmias. It is a Class Ia antiarrhythmic drug, Protein binding is 50%-65%, Hepatic

Metabolism, Route of elimination is In healthy men, about 50% of a given dose of disopyramide is excreted in the urine as the unchanged drug, about 20% as the mono-N-dealkylated metabolite and 10% as the other metabolites and Half-life is 6.7 hours (range 4-10 hours)

Comparison with available drug of same therapeutic category:

It is a quinidine like Class IA drug that has prominent cardiac depressant and anticholinergic actions, but no α adrenergic blocking property.

Disopyramide:

It's usually has no effect on sinus rate because of opposing direct depressant and antivagal actions. Prolongation of P-R interval and QRS broadening are less market. Intravenous administration of disopyramide in a dose of 1.5 - 2 mg/kg produces no measurable hemodynamic effect in patients with normal left ventricular function, but may cause a transient negative inotropic effect on the myocardium in those with abnormal left ventricular function. The drug is rapidly and almost completely absorbed from the gastrointestinal tract when taken orally. Maximum plasma levels are usually reached 1-3 hours after ingestion of a dose, and the plasma half-life of the drug is about 6 hours. The range of therapeutic plasma concentrations is 2-4 ug/ml, which may be achieved with a 100 or 150 mg dose four times a day.

Disopyramide is effective in the suppression of ventricular premature beats and ventricular tachycardia in about 80% of the patients who are placed on the therapy. It also has been successful in controlling and preventing refractory ventricular tachycardia.

Disopyramide given orally appears to be effective in the prevention of potentially serious arrhythmias in patients with acute myocardial infarction. The efficacy of disopyramide in the management of atrial tachyarrhythmias is less impressive. It has been used in the conversion of paroxysmal atrial tachycardia as well as of atrial fibrillation with a success rate ranging from 20-50%.

The rate of success for conversion of atrial fibrillation to sinus rhythm depends on the duration of arrhythmia. The conversion rate is much higher when the duration of atrial fibrillation is less than 7 days.

The drug also has been effective in controlling paroxysmal atrial tachycardia in patients with Wolff-Parkinson-White syndrome.

The therapeutic effect of disopyramide is similar to that of quinidine in the management of both ventricular and atrial arrhythmias, but disopyramide is tolerated better than quinidine by a large proportion of patients. The

recommended dose in an average person is 100 mg or 150 mg four times a day. In most patients a loading dose is not required.

The maximum daily dose should not exceed 1600 mg. In patients with renal functional impairment the daily dose requirement may be considerably curtailed. We will learn from clinical practice how to regulate the dose to fit the patients. The most significant side effects of disopyramide are caused by its anticholinergic properties.

Adverse Effect:

Disopyramide is better tolerated than quinidine, less g.i. effects. Anticholinergic side effects are the most prominent: dry mouth, constipation, urinary retention (especially in elderly males) and blurred vision. It can cause greater depression of cardiac contractility.

Cardiac decompensation and hypotension may occur in patients with damaged hearts because it also increases peripheral resistance, so that cardiac output may be markedly decreased. Contraindications are – sick sinus, cardiac failure and prostate hypertrophy.

USE:

The primary indication of disopyramide is as a second line drug for prevention of recurrences of ventricular arrhythmia. It may also be used for maintenance therapy after cardioversion of AF (Atrial fibrillation) or AFI (Atrial flutter).

AFI: - Atria beat at a rate of 200-350/min and there is a physiological 2:1 to 4:1 or higher A-V block (because A-V node cannot transmit impulses faster than 200/min). This is mostly due to a stable re-entrant circuit in the right atrium, but some cases may be due to rapid discharge of an atrial focus.

AF: Atrial fibres are activated asynchronously at a rate of 350-550/min (due to electrophysiological inhomogeneity of atrial fibres) associated with grossly irregular and often fast (100-160/min) ventricular response. Atria remain dilated and quiver like a bag of worms.

Market Formula:

Dose: 100-150 mg 6-8 hourly oral. NORPACE 100, 150 mg cap. REGUBEAT 100 mg tab.

Conclusion:

Initiation of disopyramide in the outpatient setting is safe and the risk of subsequent sudden cardiac death is low. Because of its QT-prolonging effect, precautions may be necessary in patients.

Conflict of Interest: We declared that this review does not have any conflict of interest.

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