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A REVIEW ARTICLE ON FLECAINIDE

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Abstract:

Flecainide acetate is a class IC antiarrthythamic agent and its clinical efficacy has been confirmed by the its results of several cilinical trails. Now days , flecainide is recommmened as one the first line therapies for pharmacological conversion as welll as maintenance of sinus rhythm in patient with aterial fibrillation and /or supraventricular tachycardias. Based on the caedic arrythmia suppression trail study results , flecainide is not recommened in patient with structural heart disease due to hiogt proarrthymic risk. Recent data support the role of flecainide in preventing ventricular tachyarrthyminergic polymorphic ventricular tachycardia associated both with ryanodinre receptor and calsequestrin mutation. we herein review the current clinical data related to flecainide use in clinical practice and some concerns about its role in the management of patients with coronay artery disease.

Keywords: *Atrial fibrillation: class IC anti-arrhythmic drugs: Flecinaide proarrthythmia: ventricular tachycardia.*

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INTRODUCTION:

Flecainide is a medication used to prevent and treat abnormally Fast heart rates. This includes ventricular and supra ventricular tachycardias.

Its use is only recommended in those with dangerous arrhythmia or when significant symptoms cannot be managed with other treatments. Its use does not decrease a persons risk of death. Its taken by mouth or injection into a vein.

In the recent years several non-pharmacological therapies, in particular transcatheter ablation ,particulartranscatheter ablation, have been increasingly and successfully used to treat symptomatic drug refractory patient affected by supra-ventricular arrhythmia (SVT), especially atrial fibrillation (AF) Nevertheless, anti-arrhythmic drug treatment stillplays a major role in patient management, alone or combined with non-pharmacological therapies.

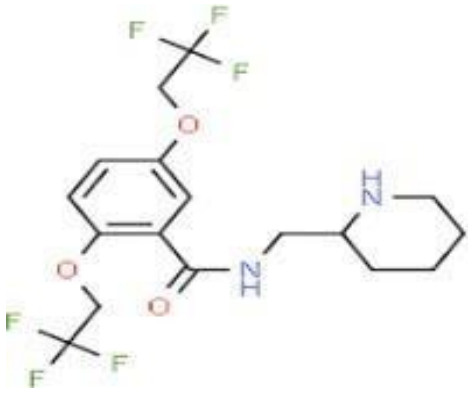
Flecainide is an IC antiarrhythmic drug approved in 1984 from the Food and Drug Administration for the suppression of sustained ventricular tachycardia (VT) and later for AF acute cardioversion and for sinus rhythm maintenance.

Currently, flecainide is mostly administered for sinus rhythm maintenance and, having regard to its effectiveness and safety profile, it may be considered underused.

The CAST study published in 1991 has strongly conditioned and limited the actual use of f lecainide in clinical practice. The study was prematurely dismissed due to excess of mortality among patients treated with IC agents with a significant great number of death and cardiac arrest due to arrhythmia than patients treated with placebo [**6**]. It is necessary to underline that many patients who died during the study had depressed left ventricular ejection fraction and intraventricular (IV) impulse disturbance, two conditions currently contraindicating the use of Flecainide.

Differently from the CAST results, recent studies, enrolling different patient populations, have demonstrated a good safety profile of the drug combined with good clinical efficacy. This review aims to highlight the main characteristics of Flecainide, as W ell as its optimal clinical use, delineating drug indications and contraindications and appropriate monitoring, based on the most recent evidence.

DRUG DISCOVERY



BRANDNAME : Tambocor
GENERICNAME ; Flecainidede
DOSAGE FORM : Tablets
FDA APPROVAL : First Approved [Aug 8 - 2023]
IUPAC : -N-[piperidin-2-yimethy]-2-5- bis [2,2,2 -trifluoethoxy] benzamide
FORMULA : C17 H20 F6 N2 O3
MOLAR MASS : 414.348 mol

The Flecainide discovery and development process started in 1966 with the broad goal of investigating the effects of fluorine substitution in potential drug molecules .The overall process evolved slowly .The original goals of the project were translated into the 3major phases:

1) The synthesis and evaluation of 2 major chemical series through the efforts of to a chemists who incorporated fluorine atoms into new compounds.

2) A change in focus from local anesthetic programs to the anti-arrhythmic projectthrough the efforts and advisement of pharmacologists.

3) Commitment to a Flecainide development plan culminating in the new drugapplication for approval of Flecainide in the suppression and prevention of ventricular arrhythmia.

FIG 1:

CHARACTERISATION OF INVESTIGATIONAL DRUG

Flecainide is a local anesthetic with five times the potency of procaine on frog nerve, with a longer duration of action. It reduces the maximum rate of depolarization in cardiac muscle at lowconcentration, both in solutions containing5.6 MM KCl and 2.8mM KCl. It has no anti-sympathetic effects, nor does antagonist the positive inotropic action of calcium on cardiac muscle. Flecainide prolonged the duration of the action potential at 90% repolarization. In guinea-piganaesthetised .

With urethane does of 5 mg/kg of F lecainide significantly increased the amount of ouabain necessary to induce heart block and ventricular arrhythmia.

Flecainide 15 mg/kg caused abnormal ventricular conduction and death in this preparation, but in pithed rats doses of 30 mg/kg of Flecainide caused no abnormalities in the electrocardiogram. Flecainide is a class 1 anti-arrhythmic drug,with very little negative inotropic or chronotropic action.

HISTORICAL APPROACHES IN DRUG DISCOVERY

Flecainide is an anti-arrhythmic medication used to treat certain types of irregularheart rhythms. Here's a brief history of Flecainide:

- 1982: Flecainide was first synthesized by scientists at Riker Laboratories, now a part of Sanofi. It was developed as a sodium channel blocker to treat cardiac arrhythmia.

- 1985: The United States Food and Drug Administration (FDA) approved Flecainidefor the treatment of documented ventricular arrhythmia.

- Over the years, Flecainide has been used to manage various types of cardiac including atrial fibrillation, atrial flutter, and supra ventricular tachycardia.

Flecainide's effectiveness and safety profile have been subjects of ongoing research and debate. It's considered a Class IC anti-arrhythmic drug and is often used when other medications have proven ineffective or have unacceptable side effects.

-Like many medications, Flecainide has specific indications and potential risks, and its use should be carefully monitored by healthcare professionals to ensure patient safety-remember that medical practices and drug regulations can change over time soit's essential to consult a healthcare provider for the most current and accurate information on Flecainide.

FORMULATION OF INVESTIGATIONAL DRUG

A bioequivalence study was performed on a new formulation of Flecanide acetate in100 mg tablets, using a formulation of the same drug already commercialized and in use and at the same dose. The study was conducted with a cross-over assay in 10healthy volunteers at a single oral dose of 200 mg (two tablets). The parameters-obtained according to the model employed, with both formulations studied, showed considerable degree of between-subject variability. The parameters showing the highest between-subject variability were KA (VC: 80.5 and 166.8%; t max, VC: 40.8 and 48.0%, and Ke, VC: 39.4 and 35.1%) for formulations A and B, respectively, the parameter with the least variability being the MRT (VC 18.7 and 21.7%) for formulations A and B.

Statistical analysis of the parameters characterizing the rate and extent to which the drug accesses to the systemic circulation, by application of statistical tests conventionally used in this kind of study- the "t" tests and ANOVA-revealed that there were no statistically significant differences among the parameters defining these processes for either formulation studied, thus permitting the assumption of bioequivalence between both formulations. The results obtained by application of the criteria of superposition and statistical moments show that there are no statistically significant differences with respect to the fraction of the dose of Flecainide administered that reaches the systemic circulation after administration of the two tablet forms studied, both containing 100mg of active principle (dose: 2 x100 mg).

A liquid pharmaceutical composition comprising Flecainide or pharmaceutically acceptable salts thereof in the range from about 1mg/ml to 20mg/ml, at least a sweetener in the range from 0.05 to 0.5% w/v, a buffer system and at least one preservative, wherein the pH of the composition is from about 5.0 to 6.5 is provided. Flecainide is preferably in the form of an acetate salt. The sweetener is preferably selected from acesulfame potassium, sucralose, cyclamate, saccharin, saccharin sodium and aspartame, in particular sucralose. The buffer system may be selected from glacial acetic acid, sodium acetate trihydrate, citric acid, sodium citrate, sodium dihydrogen phosphate, disodium phosphate, trometamol (Tris), hydrochloric acid, ascorbic acid, and sodium ascorbate as single or any combination thereof. The preferred buffer system is glacial acetic acid and sodium acetate trihydrate. The preservative is preferably selected from methyl paraben, ethyl paraben, propyl paraben, butyl paraben, isobutyl paraben, benzyl paraben, sodium benzoate, benzoic acid, potassium sorbate and combination thereof. The preferred buffer is methyl paraben. A process for the preparation of said liquid pharmaceutical composition as herein defined is also provided. A liquid composition comprising Flecainide acetate,sucralose, methyl paraben (methyl parahydroxylbenzoate) and a buffer system which comprises mixture of glacial acetic acid and sodium acetate trihydrate as herein defined is provided .

PHARMACOKINETICS ASPECT ANDDRUG DEPOSITION

Flecainide is an anti arrhythmic medication primarily used to treat certain heartrhythm disorders, such as atrial fibrillation and ventricular tachycardia. Its pharmacokinetic aspects and drug disposition involve several key factors:

1. Absorption : Flecainide is well-absorbed when taken orally. Its bioavailability can beaffected by food intake, so it's often recommended to take it on an empty stomach.

2. Distribution: Flecainide is highly protein-bound (approximately 40-50%) in the blood, primarily to albumin. This protein binding can affect its distribution in the body.

3. Metabolism: The metabolism of Flecainide occurs mainly in the liver, primarily through the CYP2D6 enzyme. Genetic variations in CYP2D6 can lead to variability in Flecainide metabolism among individuals.

4. Elimination: Flecainide is primarily eliminated via renal excretion, with a half-life ranging from 12 to 27 hours. Renal function plays a crucial role in drug clearance, and dose adjustments may be necessary in patients with impaired kidney function.

5. Drug Interactions: Flecainide can interact with other medications that affect CYP2D6 activity, potentially leading to altered drug levels and effects. important forhealthcare providers to consider potential drug interactions when prescribing Flecainide.

6.Therapeutic Drug Monitoring: Due to the variability in Flecainide's pharmacokinetics, therapeutic drug monitoring is sometimes used to ensure thatpatients within the therapeutic range, as it has a relatively narrow therapeutic window.

7. Adverse Effects: Flecainide can have pro arrhythmic effects, meaning it may worsen certain types of arrhythmia. Monitoring for side effects and adjusting thedosage is essential to minimize risks.

Flecainide is nearly completely absorbed from the gastro intestine (bioavailability: 85–90%) from 0.2 to 1 MCG/ML provide the greatest therapeutic benefit whereas value higher than 0.7 to 1 MCG/ML have been associated with increased adverse effects . The apparent volume of distribution is wide, about 40% of drug was binded to plasma proteins . Flecainide is metabolized in the liver via cytochrome (CYP2D6 and CYP1A2), and then excreted in the urine. About 30% of an orally administered dose escapes liver metabolism and is excreted in the urine unchanged . The half-life is about 20 h (range: 1227 h) and it may be prolonged until 70 h in patients with heart failure, renal disease (creatinine clearance < 50 ML/min) and liver disease It's crucial for patients prescribed flecainide to work closely with their

healthcare providers to monitor its effects and ensure its safe and effective use, considering the factors mentioned above. This information is based on knowledge available up to September 2021, and any updates or new research beyond that date may provide further insights into flecainide's pharmacokinetics and disposition

PRECLINICAL TOXICITY STUDIES AND INVESTIONAL NEW DRUG

Flecainide is a medication primarily used to treat certain heart arrhythmia. Paraclinical studies are conducted before clinical trials to assess the drug's safety andefficacy in animal models. Some key points from paraclinical studies of Flecainide might include:

1. Safety and Toxicity: Preclinical studies help determine the drug's safety profileand any potential toxic effects in animals.

2. Pharmacokinetics: Researchers examine how the drug is absorbed, distributed, metabolized, and eliminated within the body.

3. Pharmacodynamics: This involves studying how the drug affects the body'sphysiological and biochemical processes, particularly its impact on heart rhythms.

4. Dose Optimization: Finding the appropriate dosage levels that are effective whileminimizing side effects.

5. Efficacy: Assessing how well the drug works in animal models, often by inducing then measuring the drug's ability to restore normal heart rhythms.

6. Mechanism of Action: Understanding how Flecainide exerts its anti-arrhythmiceffects on a molecular level.

7. Formulation: Developing suitable drug formulations for administration (e.g., oral, intravenous).

Preclinical studies provide important insights to inform the design of clinical trialsand ensure that potential medications are safe and effective for human use.

APPLICATIONS

Flecainide is an anti-arrhythmic medication used to treat certain heart rhythm disorders, such as atrial fibrillation and ventricular arrhythmia. Here are some applications of Flecainide:

1. Atrial Fibrillation : Flecainide is often prescribed to restore and maintain normalsinus rhythm in patients with atrial fibrillation, a common irregular heart rhythm.

2. Ventricular Arrhythmia: It can also be used to manage ventricular arrhythmia, which are abnormal heart rhythms originating in the lower chambers of the heart.

3. Supra-ventricular Tachycardias : Flecainide may be used to control certain supraventricular tachycardias, including atrioventricular nodal re-entrant tachycardia (AVNRT) and atrioventricular re entrant tachycardia (AVRT).

4. Long QT Syndrome: In some cases, Flecainide can be prescribed to treat long QTsyndrome, a genetic disorder that can lead to irregular heartbeats.

5. Arrhythmia Prevention: It may be used to prevent the recurrence of certain typesof arrhythmia.

6. Off-Label Uses: In some cases, it might be used off-label for other heart-related conditions, but this should be done under the guidance of a healthcare professional.

It's crucial to use Flecainide only as prescribed by a healthcare provider due to itspotential for serious side effects and interactions with other medications. This list is not exhaustive, and the specific use of Flecainide should be determined by a medical professional.

CPCSEA GUIDELINES

GOAL

The goal of these Guidelines is to promote the humane care of animals used in biomedical and behavioral research and testing with the basic objective of providing specifications that will enhance animal well-being, quality in the pursuit of advancement of biological knowledge that is relevant to humans and animals

VETERINARY CARE

Adequate veterinary care must be provided and is the responsibility of a veterinarian or a person who has training or experience in laboratory animal sciences and medicine. Daily observation of animals can be accomplished by someone other thana veterinarian; however, mechanism of direct and frequent communication should be adopted so that timely and accurate information .

Problems in animal health, behavior, and well-being is conveyed to the attending veterinarian. The veterinarian can also contribute to the establishment of

appropriate policies and procedures for ancillary aspects of veterinary care, such as reviewing protocols and proposals, animal husbandry and animal welfare; monitoring occupational health hazards containment, and zoonosis control programs and supervising animal nutrition and sanitation. Institutional requirements will be the determine the need for full-time or par -time or consultative veterinary services.

QUARANTINE, STABILIZATION AND SEPARATION

Quarantine is the separation of newly received animals from those already in the facility until the health and possibly the microbial status of the newly received animals have been determined. An effective quarantine minimizes the chance for introduction of pathogens into an established colony. A minimum duration of quarantine for small lab animals is one week and large animals is 6 weeks (cat, dog and monkey)Effective quarantine procedures should be used for non-human primates to help limit exposure of humans zoonotic infections.Regardless of the duration of quarantine, newly received animals should be given a period for physiologic, psychological and nutritional stabilization before their use. The length of time stabilization will depend on the type and duration of animal transportation, the species involved and the intended use of the animals.Physical separation of animals by species is recommended to prevent inter species disease physiological and behavioral changes due to interspecies conflict.Such separation is usually accomplished by housing different speciesin separate rooms; however, cubicles,laminar-flow units, cages that have filtered air or separate ventilation, and is olators shall be suitable alternatives.In some instances, it shall be acceptable to house different species in the same room, for example, if two species have a similar pathogen status and are behaviorally compatible.

SURVEILLANCE, DIAGNOSIS, TREATMENT AND CONTROL OF DISEASE

All animals should be observed for signs of illness, injury, or abnormal behavior by animal house staff. As rule, this should occur daily, but more-frequent observations might be warranted, such as during postoperative recovery or when animals are ill or have a physical deficit. It is imperative that appropriate methods be in place for disease surveillance and diagnosis (Annexure 1 and 2). Unexpected deaths and signs of illness, distress, or other deviations from normal health condition in animals should be reported promptly to ensure appropriate and timely delivery of veterinary medical care. Animals that show signs of a contagious disease should be isolated from healthy animals in the colony.If an entire room of animals is known or believed
to be exposed to an infectious agent (e.g. Mycobacterium Tuberculosis in non-humanprimates), the group should be kept intact and isolated during the process of diagnosis, treatment, and control. Diagnostic clinical laboratory may be madeavailable.

ANIMAL EXPERIMENTATION INVOLVING HAZARDOUS AGENTS

Institutions should have policies governing experimentation with hazardous agents. Institutional Biosafety Committee whose members are knowledgeable about hazardous agents are in place in most of the higher level education, research institutes and in many pharmaceutical industries for safety issues. This committee shall also examine the proposal on animal experiments involving hazardous agentsin addition to its existing functions (Annexure– 8).Since the use of animals in such studies requires special consideration, the procedures and the facilities to be used must be reviewed by both the Institutional Biosafety Committee and Institutional Animal Ethics Committee (IAEC).

DURATIONS OF EXPERIMENTS

No animal should be used for experimentation for more than 3 years unlessadequate justification is provided.

PHYSICAL RESTRAINT

Brief physical restraint of animals for examination, collection of samples, and a variety of other clinical and experimental manipulations can be accomplished manually or with devices be suitable in size and design for the animal being held and operated properly to minimize stress and avoid injury to the animal.Prolonged restraint of any animal, including the chairing of non-human primates, should be avoided unless essential to research objectives. Less restrictive systems, such as the tether system or the p ole and collar system, should be used when compatible with research objectives.The following are important guidelines for the use of restraint equipments: Restraint devices cannot be used simply as a convenience in handling or managing animals.The period of restraint should be the minimum required to accomplish the research objectives. Animals to be placed in restraint devices should be given training to the equipment. Provision should be made for observation of the animal at appropriate intervals. Veterinary care should be provided if lesions or illness associated with restraint are observed. The presence of lesions, illness, or severe behavioral change should be dealt with by the temporaryor permanent removal of the animal from restraint.

PHYSICAL FACILITIES

Building materials: should be selected to facilitate efficient and hygienic operation of animal facilities. Durable, moisture proof, fire -resistant, seamles materials are most desirable for interior surface including vermin and pest resistance.

(a) Corridor(s): should be wide enough to facilitate the movement of personnel aswell as equipments and should be kept clean.

(b) Utilities: such as water lines, drain pipes and electrical connections shouldpreferably be accessible through service panels or shafts in corridors outside the animal rooms. (d) Animal room: doors should be rust, vermin and dust proof. They Should f it properly within their frames and provided with an observation window.

Door closures may also be provided. Rodent barriers can be provided in the doors of the small animal facilities.

(e) Exterior windows: Windows are not recommended for small animal facilities. However, where power failures are frequent and backup power is not available, they may be necessary to provide alternate sources of light and ventilation. In primate rooms, wind ows can be provided.

(f) Floors :Floors should be smooth, moisture proof, nonabsorbent, skid-proof, resistant to wear, acid,solvents, adverse effects of detergents and disinfectants. They should be capable of supporting racks,equipment, and stored items without becoming gouged, cracked, or pitted, with minimum number of joints.A continuous moisture -proof membrane might be needed. If sills are installed at the entrance to a room,they should be designed to allow for convenient passage of equipment.

(g) Drains :Floor drains are not essential in all rooms used exclusively for housing rodents. Floor in such rooms can be maintained satisfactorily by wet vacuuming ormopping with appropriate disinfectants or cleaning compounds. Where floor drainsare used , the floors should be sloped and drain taps kept filled with water or corrosion free mesh. To prevent high humidity,drainage must be adequate to allow rapid removal of water and drying of surfaces.

(h)Walls and ceilings: Walls should be free of cracks, unsealed utility penetrations, or imperfect junctions with doors,ceilings, floors and corners.Surface materials should be capable of withstanding scrubbing with detergents and disinfectants and the impact of water under high pressure. .

ENVIRONMENT

(a) Temperature and humidity control Air conditioning is an effective means of regulating these environmental parameters for laboratory animals. Temperature and humidity control prevents variations due to changing climatic conditions or differences in the number and kind of room occupants. Ideally, capability should be provided to allow variations within the range of approximately 18 to 29°C (64.4 to 84.2øF), which includes the temperature ranges usually recommended for common laboratory animals. The relative humidity should be controllable within the range of 30% to 70% throughout the year. For larger animals a comfortable zone (18 to 37°C)should be maintained during extreme summer by appropriate methods for cooling.

(b) Ventilation In renovating existing or in building new animal facilities, consideration should be given to the ventilation of the animals' primary enclosures. Heating, ventilating, and air-conditioning systems should be designed so that operation can be continued with a standby system. The animal facility and human occupancy areas should be ventilated separately.

(c) Power and lighting The electrical system should be safe and provide appropriate lighting and a sufficient number of power outlets. It is suggested that a lighting system be installed that provides adequate illumination while people are working in the animal rooms and a lowered intensity of light for the animals. Fluorescent lights
are efficient and available in a variety of acceptable fixtures. A time-controlled lighting system should be used to ensure a regular diurnal lighting cycle wherever required. Emergency power should be available in the event of power failure.

(d) Noise control The facility should be provided with noise free environment. Noise control is an important consideration in designing an animal facility. Concretewalls are more effective than metal or plaster walls in containing noise because their density reduces sound transmission.

ANIMAL HUSBANDRY

Caging or housing system

The caging or housing system is one of the most important elements in the physical and social environment of research animals. Itshould be designed carefully to facilitate animal well being, meet research requirements, and minimize experimental variables. The housing system should: ÿ provide space that is

adequate, permit freedom of movement and normal postural adjustments, and have a resting place appropriate to the species; (Annexure– 3) ÿprovide a comfortable environment ÿ provide an escape proof enclosure that confines animal safety ÿ provide easy access to food and water; ÿ provide adequate ventilation ÿ meet the biological needs of the animals, e.g., maintenance of body temperature, urination, defecation and reproduction .

STANDARD OPERATING PROCEDURES (SOPS) / GUIDELINES

The Institute shall maintain SOPS describing procedures / methods adapted about animal husbandry, maintenance, breeding, animal house microbial analysis and experimentation records. A SOP should contain the following items: ÿ Name of the Author ÿ Title of the SOP ÿ Date of preparation ÿ Reference of previousSOP on the same subject and date (Issue no and Date) ÿ Location and distribution of SOPS with sign of each recipient ÿ Objectives ÿ Detailed information of the instruments used in relation with animals with methodology (Model no., Serial no. and Date of commissioning) ÿ The name of the manufacturer of the reagents and the methodology of the analysis pertaining to animals ÿ Normal value of all parameters ÿ Hazard identification and risk assessment .

PERSONNEL AND TRAINING

The selection of animal facility staff, particularly the staff working in animal rooms or involved in transportation, is a critical component in the management of an animal facility. The staff must be provided with all required protective clothing (masks, aprons, gloves and gumboots and other footwear) while working in animal rooms. Facilities should be provided for change over with lockers, wash basin, toilets and bathrooms to maintain personal hygiene. It is also important a regular medical check -up is ar ranged for the workers to ensure that they have not picked up any zoonotic infection and also that they are not acting as a source of transmission of infection to the animals.

SPECIAL ARTICLE

in-charge should ensure that persons working in animal house do not eat, drink,smoke in animal room and have all required vaccination, particularly against tetanus and other zoonotic diseases. Initial in-house training of staff at all levels is essential. A few weeks must be spent on the training of the newly recruited staff, teaching them the animal handling techniques, cleaning of cages and importance of hygiene, disinfection and sterilization. They should also be made familiar with the activities of nor mal healthy and sick animals so that they are able to spot the sick animal during their daily routine check up of cages .

Anaesthesia

Unless contrary to the achievement of the results of study, sedatives, analgesics and anesthetics should be used to control pain or distress under experiment.
Anesthetic agents generally affect cardiovascular, respiratory and thermo- regulatory mechanism in addition to central nervous system. Before using actual anaesthetic the animal is prepared for anesthesia by overnight fasting and using pre-anesthetics, which block parasympathetic stimulation of cardio-pulmonary system and reduce salivary secretion. Atropine is the most commonly used anticholinergic agent. Local or general anesthesia may be used, depending on the type of surgical procedure. Local anaesthetic are used to block the nerve supply to a limited area and are used only for minor and rapid procedures. This should be carried out under expert supervision for regional infiltration of surgical site, nerve blocks and for epidural and spinal anesthesia. A number of general anesthetic agents are used in the form of inhalants. General anaesthetic are also used in the form of intravenous or intramuscular injections such as barbiturates. Species characteristics and variation must be kept in mind while using an anesthetic. Side effects such as excessive salivation, convulsions, excitement and disorientation should be suitably prevented and controlled. The animal should remain under veterinary care till it completely recovers from anesthesia and postoperative stress.

Euthanasia

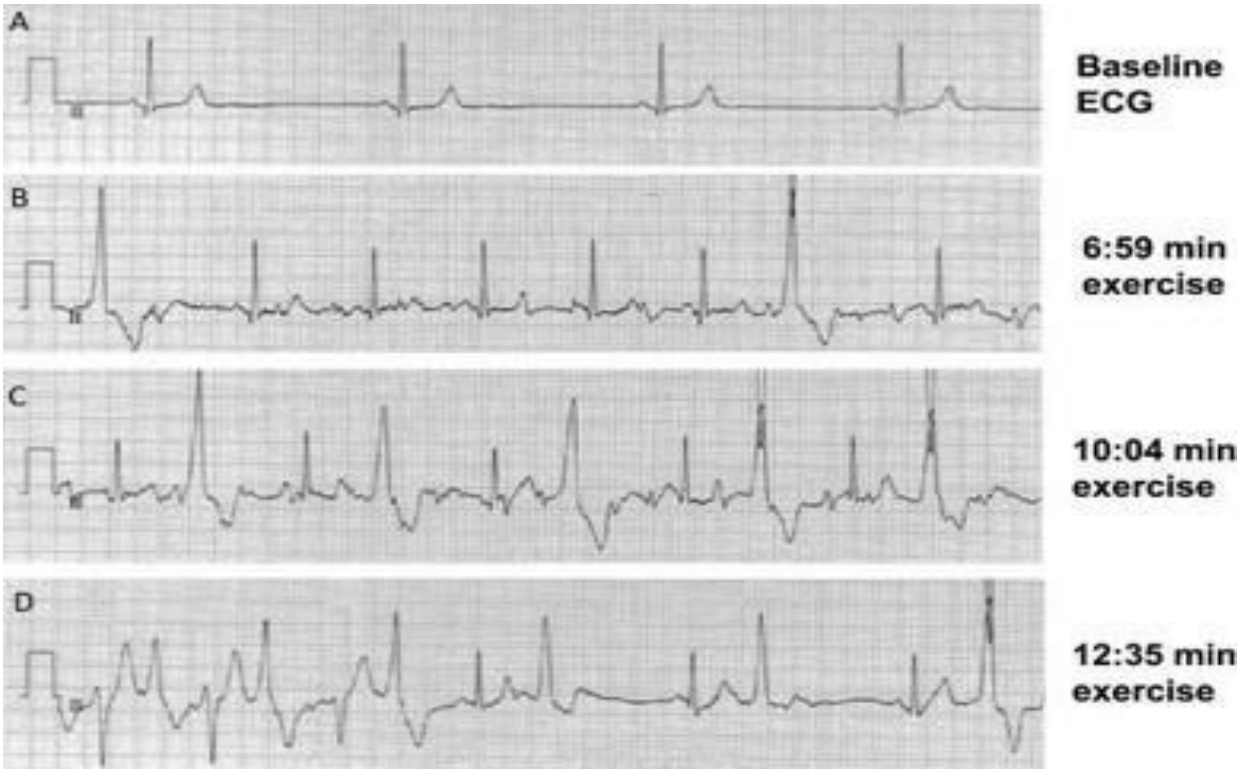
Euthanasia is resorted to events where an animal is required to be sacrificed on termination of an experiment or otherwise for ethical reasons. procedure should be carried out quickly and painlessly in an atmosphere free from fear or anxiety. For accept in g an euthanasia method as humane it should have an initial depressive action on the central nervous system for immediate insensitivity to pain. The choiceof a method will depend on the nature of study, the species of animal to be killed (Annexure– 6). Th e method should in all cases meet the following requirements: (a) Death, without causing anxiety, pain or distress with minimum time lag phase. (b) Minimum physiological and psychological disturbances. (c) Compatibility with the purpose of study and minimum emotional effect on the operator. (d) Location should be separate from animal rooms and free from environmental contaminants.

Tranquilizers have to be administered to larger species such as monkeys, dogs andcats before an euthanasia procedure.

CLINICAL TRIALS

Patients with CPVT typically present to medical attention with either stress-induced syncope or cardiac arrest, both of which will have occurred most frequently during childhood or early adolescence When left untreated, the clinical course of CPVT is severe: approximately 30% of affected individuals will experience symptoms before the age of 10 years and the majority (60%to 80%) of patients will have one or more symptom antiarrhythmic episodes before age 40 .

According to current guidelines , the clinical diagnosis of CPVT is base on the documentation of polymorphic ventricular arrhythmia that are induced by adrenergic stimuli, such as exercise or emotions, in patientswithout any other structural or electrical cardiac abnormality Since the exact number and complexity of arrhythmia sufficient for diagnosis hasnot been agreed upon yet, there still exists a certain degree of variability between individual centre in their diagnostic abilities. Even in the early reports published by Couplet al. it has been observed that arrhythmias in CPVT often appear in a uniform and reproducible pattern that facilitates the recognition of affected and is progressively overcome by a junctional automatic focus. Beyond a heart-rate of 120 -130 beats per minute, ventricular premature beats (VPB) appear that are at first isolated and monomorphic and then increase with heart-rate to quadriplegia,trigeminy, and bigeminy. Subsequently, the VPBS become polymorphic, and, finally they form bursts of non-sustained polymorphic ventricular tachycardia (VT). If the activity is stopped, the arrhythmia disappears in the reverse order without clinical symptoms. However, when the activity is continued, the arrhythmia persists and becomes more rapid, eventually assuming the appearance of polymorphic,
fibrillation -like, very fast VT that leads to syncope (Fig 2).



The hallmark sign of CPVT, highly specific but not present in all patients, is a peculiar form of polymorphic VT characterised by a 180° beat-to - beat rotation of theectopic QRS complexes that is therefore termed “bidirectional”. This arrhythmia was initially described in patients with digitalis intoxication: the drug inhibits the Na^{+}/K^{+} ATPase pump and leads to an increased concentration of intracellular sodium ions that, in

turn, results in intracellular calcium overload and the triggering of arrhythmogenic delayed after-depolarization .Experimental data suggest that bidirectional VT originates from the Purkinje cells show significantly more calcium leakage than ventricular myocytes isolated from the same heart .Despite the often unremarkable baseline ECGS foundin CPVT patients, some features may help the clinician to identify affected individuals. First, most CPVT patients show a significant sinus bradycardia in resting condition. This may be another consequence of the diastolic calcium leakage from the ryanodine receptor, facilitated by either*RyR2* or *CASQ2* mutations. An experimental study in $RyR2^{R4496C/+}$ mice showed that the intracellular calcium overload in mutant sino-atrial cells induces a slowing of the mechanism that controls the spontaneous depolarization of the so-called "calcium clock" of the heart, which determines the intrinsic beating frequency of the sinus node Second, the ECGS of CPVT patients are often characterised by prominent U waves, which are dynamic in their appearance and whose genesis and significance are not yet fully understood Finally, supra ventricular arrhythmia, including isolated atrial ectopic beats, non -sustained supra-ventricular tachycardia and bursts of atrial fibrillation, are common in CPVT Due to the dynamic nature of CPVT-related arrhythmias, exercise stress testing is the most helpful tool for the study of patientswith any clinical suspicion, since it can also help monitor the response to therapy in reproducible conditions. These tests should be complemented by 24-hours Holterrecordings, which are especially valuable in infants and younger children. In the subset of patients for whom emotions represent a more powerful arrhythmic trigger than exercise, implantable loop recorders play an important diagnostic role: they help to monitor heart rhythm for a long period of time in physiological conditions

For patients who are unable to exercise, epinephrine infusions can aid in thediagnosis of CPVT, although there are conflicting results concerning the sensitivity of this method On the contrary, programmed electrical stimulation has no diagnostic orprognostic value in CPVT, since neither bidirectional nor polymorphic VT
depends on re-entrant circuits

Genetic testing is used for diagnosis confirmation and should be offered to families of genotype -positive index cases in order to identify asymptomatic carriers of a pathogenic mutation who are considered affected according to current guidelines and should be treated even in the absence of a positive exercise stress test

NEW APPROACHES IN DRUG DISCOVERY

Atrial fibrillation is a common arrhythmia in patients with heart failure and is responsible for substantial morbidity and mortality. Restoration and preservation of sinus rhythm, therefore, has a premium. Of the numerous treatment options available, many must be avoided because of their potential for adverse effects or because of limited proof of efficacy in defined populations. Published guidelines provide help by synthesizing clinical trial data into a recommended approach. This article summarizes current information regarding the best methods applicable to patients with left ventricular dysfunction for rate control, sinus rhythm restoration and maintenance, and stroke prevention. New and evolving therapies and how they might fit into the evolving treatment paradigm are also briefly reviewed.

MATERIALS AND METHODS:

Materials All the reagents were of analytical and HPLC grade unless statedotherwise. Milli-Q-Water was used throughout the study. Hydrochloric acid, Sodium Hydroxide, Acetonitrile, sodium di-hydrogen phosphate, potassium di - hydrogen phosphate, ammonium di-hydrogen phosphate etc.(Merck, Mumbai, India) were used. Flecainide Standard was obtained as a gift sample and Flecainidetablets were purchased from Local Pharmacy.

Instrument employed

Shimadzu -1700 double beam – UV – Visible spectrophotometer with pair of 10mm matched quartz cells, Shimadzu HPLC, C18 ODS 250cmx4mmx5µm particle size column, HPLC detector is PDA, HPLC Injecting Syringe (25 ml) (HAMILTON), PH analyzer, Ultra Sonicator etc. specification of the instruments are mentioned the data givefor Electronic

Selection of solvents

The solubility of Flecainide was determined in a variety of solvents as per Indian Pharmacopoeia standards. Solubility test for Flecainide was carried out in different polar and non -polar solvents. From the solubility studies, methanol, acetonitrile was se lected solvent for proposed method.

Preparation of standard Stock Solution

100mg of Flecainide raw material was accurately weighed and transferred into the 25ml volumetric flask and dissolved in minimum quantity of mobile phase and made up to 25 ml. from this dilution 20, 40, 60, 80,100 & 120 µg/ML were made in 100 ML

volumetric flasks & make up with phosphate buffer of pH 3.0. Selection of max The solution was scanned between 200 and 400 NM range mobile phase as blank. From the UV Spectra 299nm was selected as λmax for analysis of Flecainide. Stability of the Flecainide in mobile phase was studied by measuring the same solution at this λmax in different time intervals. It was observed that Flecainide in mobile phase was stable for more than 2 hours.

Method development

Selection of chromatographic method

Proper selection of the method depends upon the nature of the sample, molecularweight, and solubility. The drug selected for the present study was polar in nature.So reversed phase chromatography can be used, this reverse phase HPLC was selected for the initial separation from the knowledge of properties, C18 column waschosen as stationary phase.

Preparation of mobile phase

0.01M solution of buffer was prepared by using water as solvent to this organic solvent acetonitrile was added. While conducting trials various buffers was used by changing the proportional of buffer and acetonitrile along with altering the PH to decide t he final development method. Then it is subjected to vacuum filtration and then proper sonication should be done which is for 15 min

Sample injection

After preparation of mobile phase, sample was prepared by taking little a quantityof mobile phase of subsequent trials in a test tube ,to this a little quantity of sample
was added and then it is sonicated. Before injecting the sample, pump is subjected to purging andthen wavelength of 299nm was adjusted then the blank was injected initially in order to get stable base line after attaining stable baseline sample was injected with syringe. Table 1: Optimized chromatographic conditions .Parameter Optimized condition Chromatograph HPLC (Shimadzu with 2487 PDA) Column
C18 ODS 250cmx4mmx5µm particle size Mobile Phase (0.01M Ammonium di-hydrogenPhosphate- pH 3.0)

BIOSTATISTICS IN PRECLINICAL STUDIES

Therapeutic trough plasma levels of flecainide associated with greater than 90% suppression of PVBS range between 200 and 1000ng/ML , although cardiac (i.e. conduction defects or bradycardia and ventricular pro arrhythmia) or non- cardiovascular adverse reactions may occur in some patients when plasma flecainide levels are 700 –1000 NG/ML . While severe adverse events have been associated at doses twice above the upper limit , they may also occur within the therapeutic plasma levels in some patients with cardiovascular diseases .

To study the relationship between plasma levels of flecainide and the suppression of
ventricular arrhythmia, a decreasing multiple oral dosage regimen (200–50 mg BID) was administered over 12days in patients with chronic VPBS . Maximum plasma levels (413 –789 NG/ML) were associated with almost complete (>95%) suppression of arrhythmia . As dose decreased, plasma levels declined to levels below about230 NG/ML that were associated with a reappearance (<70% suppression) of arrhythmia. These results suggest that the minimum range of therapeutic plasma levels of flecainide for VPBS is approximately 200–400 NG/ML and that 95%suppression of VPBS occurs at concentrations up to 800ng/ML.

In patients with supra-ventricular tachyarrhythmias treated with oral Flecainide (150– 300 mg daily), the trough plasma levels vs effect relationship was described as steep The mean serum f=Flecainide trough concentrations differed significantly between patients with and without palpitations, but the incidence of palpitations was 65% at serum flecainide concentrations <300ng/ML and 11% at 300 NG/ML,which indicates that the effective drug plasma concentrationsshould be maintained at300 NG/ML.

Salerno et al. compared the side effects with flecainide trough levels and ECG intervals in patients with ventricular arrhythmia treated with 100–200 mg BID for34 months . The incidence of adverse cardiovascular effects rose steadily with increasing flecainide plasma levels, but the maximum suppression of VPBS was achieved at flecainide plasma levels of 250–500 NG/ML . Interestingly, cardiovascular adverse effects related to drug plasma levels but not to the dose of flecainide, so to predict the occurrence of adverse effects, one must monitor some index of the concentration of the drug in plasma. As observed in Fig.1, the probability of cardiovascular adverse effects begins to rise at a plasma level of approximately750 NG/ML and reaches 50% at 1500 N G /ML. The figure also shows the percentage of patients achieving 90% suppression of VPBS at different drug plasma lev els. The correlation between both curves described the therapeutic–toxic window, which is in the range of

flecainide plasma levels between 381NG/ML (at least 50% probability of efficacy) and 710ng/mL (lessthan 10% probability of cardiovascular side effects). The risk of cardiovascular side effects increases at higher drug plasma levels, and the probability of a cardiovascular event begins to rise sharply at increases ofapproximately 40ms in both PR and QRS intervals from baseline. These resultsconfi rmed that flecainide dosing is complicated by the steepness of the dose–response for both safety and efficacy.

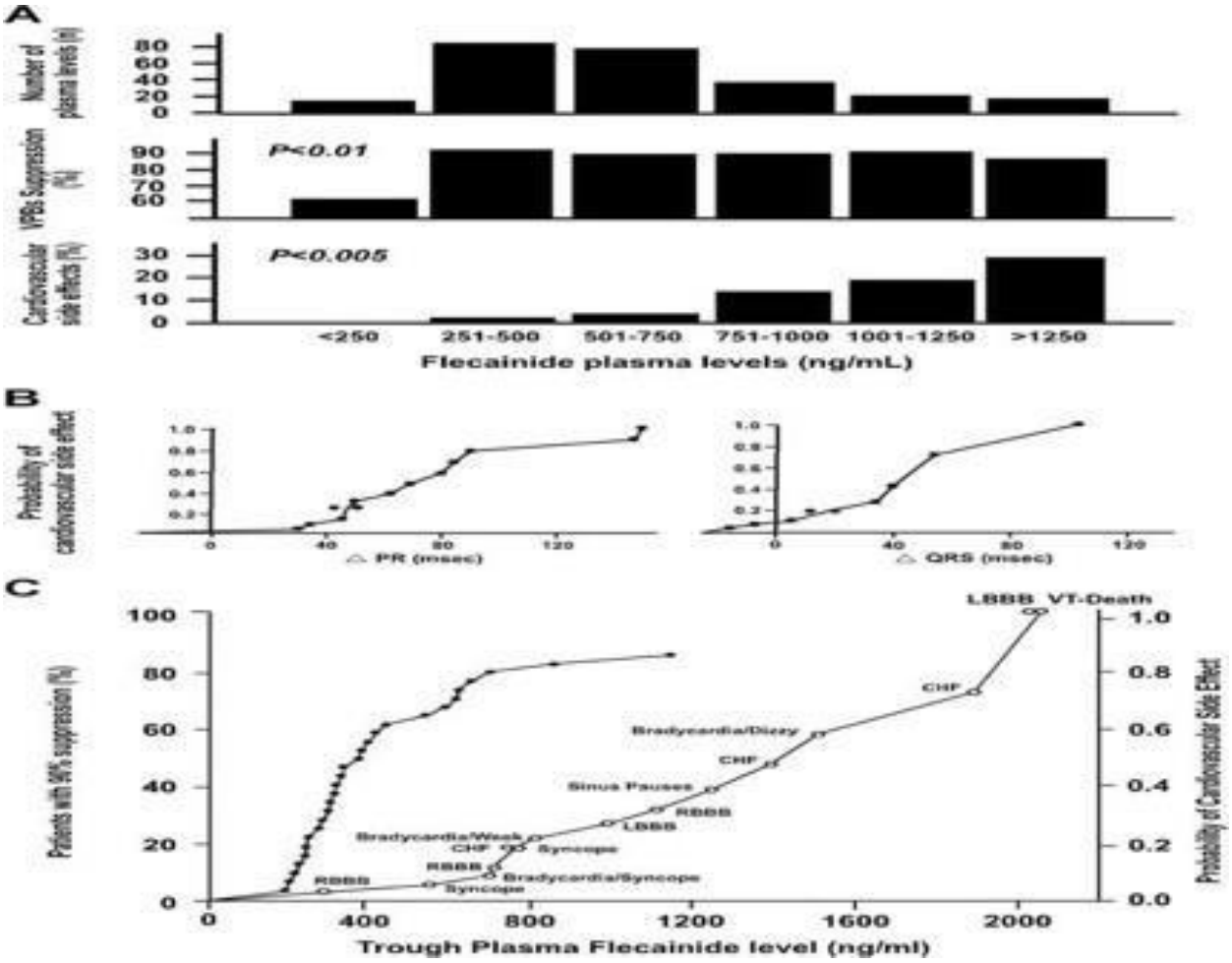


FIG3:

Considering the pharmacodynamic effects of flecainide, is not surprising that it prolongs the PR (17–29%), the QT (4–11%) interval and the QRS complex (11–27%) . It must be considered that most of the QT prolongation is due to the widening of the QRS complex, so that the JT interval and the rate-corrected QT interval remain unchanged or slightly increase (3–8%) . An important pro arrhythmic effect (3–5% of cases) is conversion of AF in atrial flutter with slow atrial rate (flutter IC) that may result in 1:1 atrioventricular (AV) conduction with high ventricular response and large QRS. Concomitant therapy with AV blockade (-blockers, verapamil, diltiazem, digoxin) could avoid this pro-arrhythmic effect . Moreover, QRS duration (>12ms), advanced kidney failure (creatinine clearance < 30 ML/min/1.73 m^2), electrolyte abnormalities increase pro-arrhythmic effect of flecainide and should be carefully monitored.

Overall, a metanalysis of 122 prospective studies demonstrated that in patientt with SVT and no significant LV impairment, pro arrhythmic events were significantly lower with flecainide than placebo (2.7% vs. 4.8%;$p < 0.001$) without significant differences in terms of total mortality .

Lastly, due to flecainide effect on the Na channels, the major non-cardiac side effectsare related to its anesthetic properties; the most frequent are dizziness

and visual disturbances while headache, gastrointestinal disturbances and metallic taste.

Patients with Pacemaker and Implantable Cardioverter Defibrillator

In the last few years, use of implantable cardiac electronic devices has become increasingly common and at least 50% of these patients may develop AF requiring anti-arrhythmic therapy . Early raised issue of negative effects of flecainide on pacing and defibrillation threshold are not a concern anymore due to progress in lead technology, automatic setting of pacemaker output and use of biphasic high energy shocks. On the other hand, antiarrhythmic drugs may enhance rhythm control in patients with pacemaker and AF in a hybrid approach . Borini demonstrated that use of flecainide was associated with lengthened atrial tachycardia cycles and consequently higher atrial anti -tachycardia pacing efficacies . This effect was probably correlated either to prolongation of atrial wavelength or widening of the temporal excitable gap during AF. Atrial anti-tachycardia pacing cannot terminate AF, but it can terminate atrial tachycardia episodes that are the first step in AF disease history .

For these reasons, flecainide administration could increase atrial anti-tachycardia pacing efficacy that represented an independent predictor of permanent or persistent
AF risk.

Otherwise, in patients with VT and implantable cardioverter defibrillator, flecainide may induce lengthening of cycle length of VT due to IV conduction delay resulting in out of -window VT which will not be treated by defibrillator. On the contrary, in case of SVT, enlargement of QRS morphology induced by flecainide may result in inappropriate shocks .

Plasma levels and side effects of flecainide acetate. **a** Flecainide plasma levels,per centsuppression of VPCS from pretreatment and per cent of plasma levels associated with cardiovascular side effects for flecainide plasma levels grouped in250-ng/ML increments. **b** The probability of cardiovascular side effects compared with the change in ECG intervals from baseline ($n = 40$ for PR and $n = 36$ for QRSinterval). Bundle branch block was excluded from analysis for comparison of change in QRS interval with cardiovascular side effects.**c** The probability of cardiovascular-side effects occurring is compared with trough plasma flecainide levels by use of the Kaplan–Meier product limit estimator for all 43 patients (*open circles*). The efficacy/plasma concentration curve for 90% suppression of VEDS is also shown for those 33 patients with available data for both efficacy and flecainide levels (*closed symbols*).Twenty -eight of the 33 patients achieved at least 90% suppression of VEDS. *RBBB* right bundle branch block,*CHF* congestive heartfailure, *LBBB* left bundle branch block, *VPBS* premature ventricular beats, *VT* ventricular trachycardia(taken from Salerno et al.)

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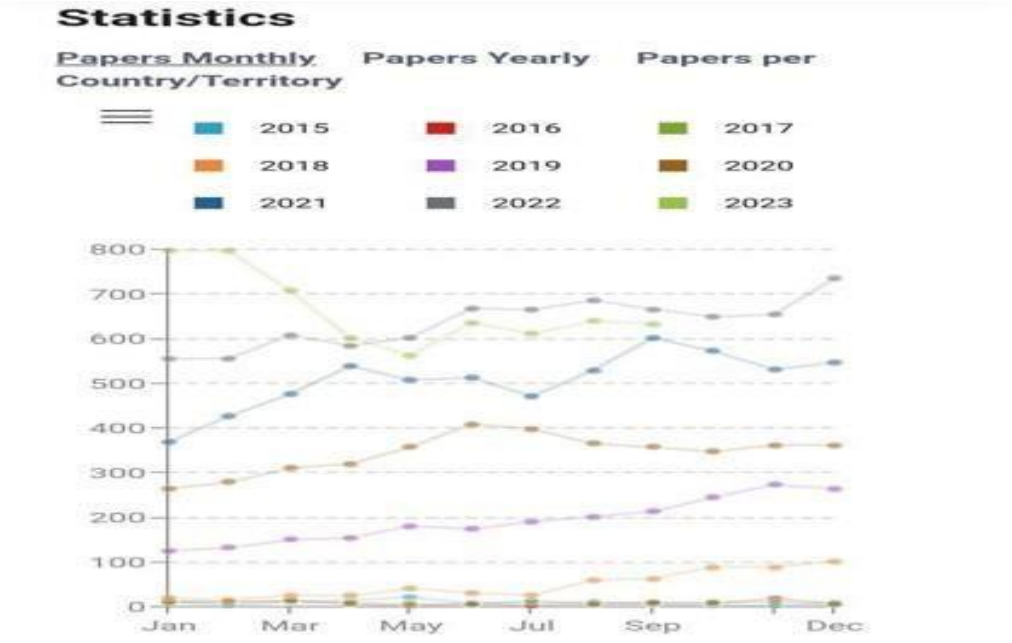

REFERENCES:

1. *"Flecainide Acetate Monograph for Professionals"* . *Drugs.com. American Society ofHealth-System Pharmacists . Retrieved 7 April 2019.*
2. ^ Jump up to:***a b c*** *British national formulary : BNF 76 (76 ed.). PharmaceuticalPress. 2018. p. 103. ISBN 9780857113382.*
3. *^ "Flecainide (Tambocor) Use During Pregnancy" . Drugs.com . Retrieved*
4. Hindricks, G.; Potpara, T.; Dagres, N.; Arbelo, E.;Bax, J.J.; Blomström-Lundqvist, C.; Boriani, G.; Castella, M.; Dan, G.-A.; Dilaveris, P.E.; et al. 2020 ESC Guidelines for the Diagnosis and Management of Atrial Fibrillation Developed in Collaboration with the European Association of Cardio-Thoracic Surge ry (EACTS). *Eur. Heart J.* **2020**, ehaa612.Rocca, D.G.; Mohanty, S.; Trivedi, C.; Biase, L.D.; Natale, A. Percutaneous Treatment of Non -Paroxysmal Atrial Fibrillation: A Paradigm Shift from Pulmonary Vein to Non-Pulmonary Vein Trigger Ablation?*Arrhythm. Electrophysiol. Rev.* **2018**, *7*, 256.
5. Nieuwlaat, R.; Capucci, A.; Camm, A.J.; Olsson, S.B.; Andresen, D.; Davies, D.W.; Cobbe, S.; Breithardt, G.; Le Heuzey, J.-Y.; Prins, M.H.; et al. Atrial Fibrillation Management: A Prospective Survey in ESC MemberCountries. *Eur. Heart J.* **2005**, *26*, 2422–2434.
6. Saksena, S.; Slee, A.; Waldo, A.L.; Freemantle, N.; Reynolds, M.; Rosenberg, Y.; Rathod, S.; Grant, S.; Thomas, E.; Wyse, D.G. Cardiovascular Outcomes in the AFFIRM Trial (Atrial Fibrillation Follow-Up Investigation of Rhythm Management). *J. Am. Coll. Cardiol.* **2011**, *58*, 1975–1985.
7. Allen LaPointe, N.M.; Dai, D.; Thomas, L.; Piccini, J.P.; Peterson, E.D.; Al - Khatib, S.M. Comparisons of Hospitalization Rates Among Younger Atrial Fibrillation Patients Receiving Different Antiarrhythmic Drugs. *Circ. Cardiovasc. QualOutcomes* **2015**, *8*,292–300.
8. Echt, D.S.; Liebson, P.R.; Mitchell, L.B.; Peters, R.W.; Obias-Manno, D.; Barker, A.H.; Arensberg, D.; Baker, A.; Friedman, L.; Greene, H.L.; et al. Mortality and Morbidity in Patients Receiving Encainide, Flecainide, or Placebo: The Cardiac Arrhythmia Sup pression Trial. *N. Engl. J. Med.* **1991**, *324*, 781 –788.
9. Conard, G.J.; Ober, R.E. Metabolism of Flecainide.*Am. J. Cardiol.* **1984**, *53*, B41 B51.
10. Anderson, J.L.; Stewart, J.R.; Perry, B.A.; Van Hamersveld, D.D.; Johnson, T.A.; Conard, G.J.; Chang, S.F.; Kvam, D.C.; Pitt, B. Oral Flecainide Acetate for the Treatment of Ventricular Arrhythmias'. *Engl. J. Med.* **1981**, *305*, 473 –477.
11. Tjandra -Maga, T.; Verbesselt, R.; Hecken, A.; Mullie, A.; Schepper, P.Flecainide: Single and Multiple Oral Dose Kinetics, Absolute Bioavailability and Effect of Food and Antacid in Man.*Br. J. Clin. Pharmacol.* **1986**, *22*, 309–316.
12. Holmes, B.; Heel, R.C. Flecainide A Preliminary Review of Its Pharmacodynamic Properties and Therapeutic Efficacy.*Drugs* **1985**, *29*, 1–33.
13. Josephson, M.A.; Ikeda, N.; Singh, B.N. Effects of Flecainide on Ventricular Function: Clinical and Experimental Correlations. *Am. J. Cardiol.* **1984**, *53*, B95 – B100.
14. Campbell, T.J.; Williams, E.M.V. Voltage- and Time -Dependent Depression of Maximum Rate of Depolarisation of Guinea -Pig Ventricular Action Potentials by Two New Antiarrhythmic Drugs, Flecainide and Lorcainide.*Cardiovasc.Res.* **1983**, *17*, 251–25
15. Moss AJ, Schwartz PJ, Crampton RS,*et al* The long QT syndrome. Prospective longitudinal study of 328 families*C.irculation* 1991;84: 1136–1144.
16. Splawski I, Shen J, Timothy KW,*et al* Spectrum of mutations in long-QT syndrome genes. KVLQT1, HERG, SCN5A, KCNE1, and KCNE2. *Circulation* 2000;102: 1178–1185.
17. Plaster NM, Tawil R, Tristani-Firouzi M, *et al* Mutations in Kir2.1 cause thedevelopmental and episodic electrical phenotypes of Andersen's syndrome .*Cell* 2001;105: 511–519.
18. Mohler PJ, Schott JJ,Gramolini AO,*et al* Ankyrin -B mutation causes type 4 long- QT cardiac arrhythmia and sudden cardiac death*N ature* 2003;421: 634–639.
19. Dumaine R, Wang Q, Keating MT,*et al* Multiple mechanisms of Na+ channel- linked long -QT syndrome .*Circ Res* 1996;78: 916–924.
20. Schwartz PJ, Priori SG, Locati EH, *et al* Long QT syndrome patients with mutations of the SCN5A and HERG genes have differential responses to Na+ channel blockade and to increases in heart rate. Implications for gene-specific therapy (see comments) *Circulation* 1995;92: 3381–3386.

21. Rosero S, Zareba W, Robinson JL,*et al* Gene - specific therapy for long QT syndrome: QT shortening with lidocaine and tocainide in patients with mutation of the sodium channel gene.*Ann Noninvasive Electrocardiol*1997;2: 274–278.
22. Benhorin J, Taub R, Goldmit M,*et al* Effects of flecainide in patients with new SCN5A mutation: Mutation-specific therapy for long-QT syndrome? *Circulation* 2000;101: 1698–1706.
23. Windle JR, Geletka RC, Moss AJ, *et al* Normalization of ventricular repolarization with flecainide in long qt syndrome patients with scn5a:deltakpq mutation *Noninvasive Electrocardiol* 2001;6: 153–158.
24. Nagatomo T, January CT, Makielski JC.Preferential block of late sodium current in the LQT3 DeltaKPQ mutant by the class I(C) antiarrhythmic flecainide *Pharmacol* 2000;57: 101–107.
25. Echt DS, Liebson PR, Mitchell LB*et al* Mortality and morbidity in patients receiving encainide, flecainide, or placebo. The Cardiac Arrhythmia Suppression Trial. *N Engl J Med* 1991;324: 781–788.
26. Antzelevitch C.The Brugada syndrome: Ionic basis and arrhythmia mechanisms .*J Cardiovasc Electrophysiol*2001;12: 268–272. Chen Q, Kirsch GE, Zhang D,*et al* Genetic basis and molecularmechanism for idiopathic ventricular fibrillation*Nature* 1998;392: 293–296.
27. Bezzina C, Veldkamp MW, Van Den Berg MP,*et al* A single Na(+) channel mutation causing both long-QT and Brugada syndromes 1213. *C.irc Res* 1999;85: 1206–
28. Veldkamp MW, Viswanathan PC, Bezzina C,*et al* Two distinct congenital arrhythmias evoked by a Mult dysfunctional Na(+) channelE97. *Ci.rc Res* 2000;86: E91.
29. Priori SG, Napolitano C, Schwartz PJ,*et al* The elusive link between LQT3 and Brugada syndrome: The role of flecainide challenge *Ci.rculation* 2000;102: 945–947.
30. Bennett PB. Long QT syndrome: Biophysical and pharmacologic mechanisms in LQT3. *J Cardiovasc Electrophysiol*2000;11: 819–822.
31. Abriel H, Wehrens XH, Benhorin J,*et al* Molecular pharmacology of the sodium channel mutation D1790G linked to the long-QT syndrome921–*C. irculation* 2000;102:925.
32. Wehrens XH, Abriel H, Cabo C,*et al* Arrhythmogenic mechanism of an LQT-3 mutation of the human heart Na(+) channel alpha-subunit: A computational analysis 20 .*Circulation* 2000;102: 584–590.