Flecainide Acetate: Its multiple diagnostic-therapeutic uses and value in Brugada Syndrome and in the Lqt3 Variant

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FLECAINIDE ACETATE
Structure. Figure 1.

Pharmacokinetics: its absorption is around 90% and is not affected by food or antiacid agents. The balanced state is obtained after 5 to 7 days.

Plasma transportation: 50% to 70% bound to plasma proteins.

Therapeutic plasma concentration: from 0.2mg/ml to 0.8m/ml up to 1 mg/ml (up to 100mg/ml). Above this value, a toxicity sign could arise; however, in sensitive patients toxicity manifestations could occur in lower values.

T½ (half life): it depends much on urine pH. If acidified 10h and if alkalized 17h. In average from 8h to 14h (mean 11.3h). It increases in renal insufficiency.

Organs that metabolize the drug:

Liver: 60%. Mediated in a polymorphic way by the P450 2D6 enzyme, producing inactive metabolites and meta-O-delkylate-flecainide with a 20% activity of the drug.

Patients with poor CYP2D6-mediated metabolism (heterozygous -EMs and intermediate and poor metabolizers) showed age-related reduction in flecainide metabolism because metabolism was taken over by CYP1A2, whose activity decreases with age [1]

Kidneys: 30% to 40%. It could be eliminated unaltered. This via is enough to eliminate the drug. It is not removed by dialysis. Its binding with plasma proteins decreases in renal insufficiency. A poor understanding of the elimination routes for anti-arrhythmic drugs and the risks involved when combined with nonsteroidal anti-inflammatory drugs modifying glomerular hemodynamics can lead to dangerous prescriptions and life-threatening situations in patients on multiple drug regimens [2]

Maternal milk. Based on the pharmacokinetics of flecainide in infants, the expected average steady-state plasma concentration of flecainide in a newborn infant consuming all of the milk production of its mother (approximately 700 ml/day) would not be expected to exceed about 62 ng/ml [3].

Useful therapeutic plasma concentration range: 0.2 to 0.8 mg/ml.

Mechanism of action-pharmacokinetics:
It belongs to class IC of the Vaughan Williams classification. IC (flecainide, propafenone, encainide, moricizine and lorcanide) that has a strong blocking effect on the Na⁺ channel and slow binding and dissociation kinetics (10 seconds to 30 seconds) with this channel (in vitro 12.9 to 21 seconds). This depression of V max is rate-dependent and with a more intense negative dromotropic
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effect.

The class IC is differentiated from the 1A class by having a more intense negative dromotrophic effect, barely affecting action potential (AP) duration, and being able to prolong refractoriety minimally.

It shortens AP in Purkinje fibers (probably by delayed gating Na⁺ channel block) and on the contrary, it prolongs AP in the muscle fibers of ventricles and atria (possibly by block of delayed rectifier currents) [4]. In the latter, the drug prolongs AP significantly at high heart rates; unlike quinidine that prolongs AP at slow rates [5]. Flecainide and quinidine increase AP duration (APD) in the human atrial tissue; however, with an opposite dependence on HR. The effect of the drug increasing APD and refractoriety at high rates is very useful in AF reversion with a high rate of ventricular response. The mechanism by which it acts reversing AF is by prolonging that of the atria.

Sarcolemmal channels affected (blocked) by the drug

- **Na⁺ fast channel**: strong effect with slow binding and dissociation kinetics. It thus decreases to \( V_{max} \) the amplitude of phase 0, and consequently conduction velocity. The Na⁺ channel block caused by this drug is processed as a repetitive activity on the same phenomenon known as use-dependent block (UBD) [6].
- **Ito1 channel**: it blocks this channel in therapeutic concentrations, independently from the rate, unlike quinidine. This channel usually recovers fast from the inactivation state (more in humans than in dogs), and thus contributes in fast rates repolarization. Pharmacological sensibility to the \( I_{to1} \) channel block of the drug is much higher in humans than in dogs [7].
- **I_{Kr}^{−2+}**: the inhibition of this channel occurs only in high concentrations. Through this mechanism, class I antiarrhythmic agents decrease Ca²⁺ overload, what in the short run may remove arrhythmias by triggered activity in clinical practice [8].
- **Delayed rapid rectifier potassium current \( I_Kr \)**: [9]: the block in the delayed rapid rectifier K⁺ current by flecainide is voltage-dependent and is similar to the interaction observed between this drug and the Na⁺ channel. E.g.: depolarization increases the degree of block while repolarization leads to a removal of it [10]. Flecainide causes fast inhibition of the rectifier potassium channel (\( IKr \)) in the open state, in a sustained way during depolarization, similarly to quinidine and propafenone. The inhibition power is the same as for quinidine (class IA) and propafenone (class IC), somehow lower for flecainide and still lower for lidocaine (class IB) [11].

Negative inotropic effect: present. It could precipitate CHF in patients with ventricular performance involvement in 16% of the cases an in 6% of those with heart failure. They could be employed in cases of diastolic heart failure and arrhythmia.

Effect on accessory pathways: they prolong the refractory period reducing the return of stimuli to the atria.

Brand name: Tambocor®

Presentation: pills with 100 mg and 1 ml ampoules with 10mg/ml.

Dosage and ways of administration

**Oral**: the initial dose advised is 50 to 100 mg 2 x day. Each 4 days it is increased in 50 mg until control. Maximal dose 200 mg 2 x day (300 to 600 mg daily);

**IV**: 1.4 mg/kg in 5 minutes or 2mg/kg for 30 minutes followed by continuing infusion in a rhythm of 0.1-0.25 mg/Kg/hour.

In the protocol for Brugada syndrome (BrS) diagnosis, it is used in a dose of 2 mg/kg IV bolus in more than 10 minutes.

**Cordocentesis**: in fetal arrhythmias. Maternal PR and QRS intervals must not exceed 140% of basal value.

Effect of the drug on the ECG

**Sinus rate**: it is not modified in normal conditions. In the presence of prior sinus dysfunction it could diminish and even cause sinus arrest.

**PR interval**: it is prolonged by increase of AH and HV intervals.

**QRS interval**: it is prolonged. Prolongation of QRS complex may be observed in therapeutic concentrations with class IC drugs.

**QT interval**: it is prolonged. After the administration of flecainide in a patient carrier of BrS, the appearance of a positive test was associated to QTc interval prolongation located in the right precordial leads [12]. The Na⁺ channel block with flecainide decreases QT interval prolongation in the LQT3 variant of congenital LQTS.

**JT interval**: it is not modified

**ST segment**: bibliography reports the case of a male patient in whom EV treatment on a paroxysmal AF carrier, caused ECG alterations similar to those of acute septal infarction. A rushed ECG evaluation did not reveal a segmentary alteration in the left ventricle and serum enzymes remained normal, and for all of these reasons thrombolytic therapy was not carried out. An afterwards study revealed this to be a latent form of BrS [13].

**Indications:**

- **Diagnostic**

Therapeutic

**A) Diagnostic**: **In Brugada syndrome:**

Patients with BrS or suspected mutation carriers can have normal ECG recordings at other times. ECG patterns may be dynamic, where changes may resolve to baseline or one particular type may evolve into another. In suspected cases without spontaneous demonstration of type 1 Brugada ECG pattern, a diagnostic challenge with a sodium channel blocker such as ajmaline, flecainide, or pilsicainide may induce the full-blown type 1 ECG Brugada pattern and support the diagnosis [14]. Class I antiarrhythmic drug
Infusion has been established as the standard test to unmask BrS, additionally, Induced Brugada-type 1 ECG is a sign for imminent malignant arrhythmias [15].

A rest 12-lead ECG is recorded previously, with the high right accessory leads (V1A and V2A), and an ECG with the same characteristics is recorded after the administration of flecainide 2 mg/kg of body weight, EV in more than 10 minutes.

Flecainide overdose can cause a type 1 ECG Brugada pattern on ECG in a previously well patient [16].

The test with flecainide using only the 12 conventional leads could be negative in patients carriers of BrS, and that only becomes positive by recording the high right precordial leads. Therefore, a negative flecainide test does not rule out the presence of the syndrome if only the classical 12 leads were applied [17].

The provocative test should be performed in an environment with the necessary equipment for cardiopulmonary resuscitation, because in 0.5% of the cases ventricular fibrillation is liable to occur. If necessary, the previous authorization of the test by the local committee of ethics should be sought. Ventricular asystole may occur and is significantly higher in patients who were proved to be carriers of the SCN5A mutation, even when they were asymptomatic [18]. Unrecognized SCN5A mutations could underlie class IC-induced sinus arrest and conduction defects in some patients [19]. The diagnostic test is indicated in concealed or intermittent forms, and in patients carriers of ECG patterns type 2 and 3 to clarify the diagnosis. THE TEST IS NOT INDICATED IN SPONTANEOUS TYPE 1 ECG BRUGADA PATTERN.

Note: Patients carriers of the type 1 ECG pattern, do not have an indication to conduct the test, since it does not add any other valuable data.

### Positive criteria for the pharmacological test:

The pharmacological test is considered to be positive, in the following circumstances:

- If an additional 1mm elevation of the ST segment appears in the V1, V2 leads or from V1 to V3 with duration of at least 80 ms after the J point.
- A J wave with a > 2 mm amplitude from V1 to V3 without RBBB pattern if the rest of the tracing is almost ECG;
- Type 2 or 3 conversion for type 1;
- Simultaneous ST segment elevation in the right precordial and inferior leads [20]. There have been reports of elevation only in the inferior wall, simulating diaphragmatic ischemia [21]. We think that this response must be considered a positive test.
- A transformation from ECG type 3 into type 2 is not considered positive; however, it is in the presence of syncope [22,23]. According to Naccarela, using this drug in oral administration, with diagnostic purposes, it showed 70% sensitivity, probably by a slow binding and dissociation kinetics with the sodium channel.

### Usefulness of the test:

As diagnostic test to unmask concealed or intermittent forms of BrS and in differentiation with genuine idiopathic fibrillation.

**Reproducibility:** The flecainide test reproducibility is very high, however, eventually patients with BrS have positive flecainide have not reproducible in a subsequent test [24].

### Sensitivity and Specificity

The sensitivity and specificity, calculated in SCN5A-positive probands and their family members, were 77% and 80%, respectively. Flecainide testing is a valid and safe tool to identify SCN5A-related BrS patients. Baseline ECGs do not predict test outcomes, but point to conduction slowing as a core mechanism in BrS [25]. Disparate response of Brugada patients to flecainide and ajmaline, with a failure of flecainide in 7 of 22 cases (32%). A type 1 Brugada ECG pattern was induced or enhanced in 22 of 22 patients following ajmaline administration. Greater inhibition of I(to) by flecainide may render it less effective. These observations have important implications for identification of patients at risk for sudden death [26]

Blockade with type IC antiarrhythmics can provoke characteristic ECG changes consistent with type 1 Brugada ECG pattern in unselected patients with atrial fibrillation. From 176 treated patients, the incidence of the characteristic abnormality was observed in 2.3% of cases [27].

In dog animal model, combined sodium and calcium channel block may be more effective than sodium channel block alone in unmasking the BrS and that pharmacologic agents that inhibit I(to) may be useful in preventing lethal arrhythmias in patients with the BrS [28].

### B) Therapeutics indications

- First choice for acute conversion of AF in absence of structural heart disease with involvement of performance (For this purpose, other equally efficient drugs are dofetilide, propafenone, amiodarone, quinidine) [29];
- Flecainide is an important addition to the therapeutic armamentarium because it is a potent agent for the treatment of paroxysmal supraventricular tachycardia in patients without structural heart disease. Leclercq et al [30] published a study on the use of flecainide in cardioversion (CV) of atrial tachyarrhythmias. After electric CV, 98% of the patients using flecainide previously were converted, against 78% of controls (P < 0.01). Experimentally in animals, flecainide increases the defibrillation threshold, but in spite of this, when administered before CV it has a beneficial effect; For Lone Atrial Fibrillation [31];
- Prevention of recurrence in patients with symptomatic supraventricular tachycardia [32];
- In short-term prevention of supraventricular paroxysmal tachycardia and paroxysmal AF [33];
- In AF to maintain sinus rhythm in patients without structural heart disease, as first line therapy, used after disopiramide, dofetilide, sotalol or amiodarone, if necessary; In atrial flutter that occurs after the Fontan procedure. This arrhythmia is frequently badly tolerated. The drug could bring some benefit as well as digoxin, amiodarone and propafenone. Patients treated with these drugs or antichagycardia pacemaker respond approximately in 50% of the cases. Faced the failure of these steps Balaji et al [34] suggest the option of atrietomy, His bundle ablation or flutter ablation;
- By corderosintesis is probably the treatment of choice for fetal high-risk supraventricular and ventricular arrhythmias, with severe fetal edema. The drug does not possess teratogenic effects and it goes through the placenta at an 80% level against the maternal one. It could present some risk of fetal death. The prognosis is poor when there is hydrops fetalis [35];
- Flecainide may be useful in patients with debilitating nonsustained ventricular arrhythmias in the absence of structural heart disease [36];
- Flecainide is used Na+ channel block with this drug has been proposed for the treatment of the LQT3 as long-term treatment for LQT3 since it shortens the QT interval. In some LQT3 patients, this drug causes Brugada-like ST segment elevation (intermediary phenotype) [37]. There were 13 carriers of the LQT3 variant tested with EV flecainide in a
dose advised for the pharmacological test in BrS. In 12, QTc interval shortening was observed, and in 6 out of 13, ST segment elevation from V1 to V3 ≥ than 2 mm [38]. Phenotypic overlap of LQT3 with BrS is observed in some carriers of mutations in the Na channel SCN5A. In the SCN5A gene, the mutation in the Na+ channel DeltaKPQ causes LQT3, and the 1795insD mutation causes both: BrS and LQT3. The last mutation, with use of flecainide in use-dependent mode lasts 4 times the recovery from the inactivated state by enhancing intermediary inactivation. Both mutations with the use of flecainide cause modifications in the gates of inactivation from the closed state, with fast and intermediary inactivation [39]. A low dose of oral flecainide shortens the QTc interval and normalizes the T wave repolarization pattern in patients with the LQT3 variant with the DeltaKPQ mutation of SCN5A. The DeltaKPQ mutation presents repetitive reopening of Na+ channel and a slow and prolonged cation-entrance current in phase 2 [40]. This current manifests in ECG by QT interval prolongation at the expense of the ST segment and a delayed appearance of T wave. Flecainide acting on the Na+ channel with the DeltaKPQ mutation causes a preferential block in the delayed Na+ entrance current with slow recovery, which explains the QT interval shortening in the LQT3 variant [41]. Thus, flecainide in low doses is a promising therapeutic agent for patients with LQTS with the DeltaKPQ mutation of SCN5A in the Na+ channel. It was verified that only flecainide (and not lidocaine) corrects the LQT3 phenotype in DG mutation carriers. These results prove that this mutation confers a unique pharmacological response in the expression of the channels, and it is known that the DG channels block by flecainide acts on the C-terminal of the alpha subunit of the Na+ channel by a flecainide/channel interaction. A negative shift of steady-state Na channel inactivation and enhanced tonic block by class IC drugs represent common biophysical mechanisms underlying the phenotypic overlap of LQT3 and BrS with E1784K mutation in SCN5A and further indicate that class IC drugs should be avoided in patients with Na channels displaying these behaviors [42]. Oral flecainide can induce syncope in patients with known LQT3 [43].

Contraindications [44,45].

Involved ventricular function; AV block; SA node disease and bradycardia.

Side effects

- Non cardiac
  - Neurological: dose-dependent blurred vision (the most frequent non cardiac side effect), headache, ataxia, dizziness, mental confusion, irritability.
  - Gastrointestinal: nausea, vomiting, diarrhea.
- Cardiac

Proarrhythmia: worsens preexisting dromotropic disorders, particularly in those with preexisting disease of conduction system; in the presence of prior sinus dysfunction, it may cause sinus arrest [46].

Appearance of new arrhythmias or worsening of those already existing: present in 5% to 30% of cases; increase of ventricular rate in patients with flutter, reentrant ventricular tachycardia.

Experimentally in dogs, Krishnan and Antzelevitch [47]verified that flecainide induces repolarization dispersion in ventricular wall thickness by causing marked APD shortening in the epicardium, and almost nothing in the endocardium, predisposing the appearance of extra-systole activity by the mechanism described by them, called "reentry in phase 2".

The drug causes a negative predominant dromotropic effect in high rates. It increases the occurrence of proarrhythmias in post-infarction patients, especially non-Q infarction. In this group, it should not be employed because it increases mortality [48]. In patients, with ejection fraction under 30%, clinical efficacy and tolerance were significantly lower, with CHF worsening in patients with prior involvement of the pump, decreasing ejection fraction in these even more [49].

Side effects in pregnancy for the binomial mother/fetus

FDA risk category: C
Mother/fetus relationship: 0.24-1.4
Milk/plasma: removal by maternal milk

Medication interaction

The following drugs increase the serum concentration of this drug:

- Propranolol
- Amiodarone
- Quinidine
- Fluoxetine (it inhibits the isoenzyme of cKDOCromo P450IID6)
- Paroxetine Supratherapeutic flecainide plasma concentrations may cause delirium. Because toxicity may occur when flecainide is prescribed with paroxetine and other potent CYP2D6 inhibitors, flecainide plasma concentrations should be monitored closely with commencement of CYP2D6 inhibitors [50].

References


CV of the author
- Profesor Asociado de la Escuela de Medicina ABC de San Pablo, Brasil
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