Flecainide

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Flecainide is an IC antiarrhythmic drug approved in 1984 from Food and Drug Administration for the suppression of sustained ventricular tachycardia and later for acute cardioversion of atrial fibrillation (AF) and for sinus rhythm maintenance. It is categorized as a Vaughn-Williams Class IC agent based upon its properties of causes a strong degree of sodium channel blockage with slowing cardiac conduction and a minimal effect on ventricular repolarization. Currently, flecainide is mostly used for sinus rhythm maintenance in atrial fibrillation patients without structural cardiomyopathy although recent studies enrolling different patient population demonstrated a good effectiveness and safety profile.

flecainide | flecainide controlled-release | atrial fibrillation | CAST | supraventricular arrhythmias

1. Introduction

Flecainide is a class IC antiarrhythmic drug (AAD). Flecainide was first synthesized in 1972 and approved in 1984 from the Food and Drug Administration (FDA) for the suppression of sustained ventricular tachycardia [1] and later for acute cardioversion of AF and for sinus rhythm maintenance. Currently, the use of flecainide in atrial fibrillation represents the main indication of the drug. Nevertheless, despite its effectiveness and safety profile it is still underused [2]

Pharmacokinetics

Flecainide, administered bis in die (immediate-release form) or once daily (controlled-release form), is nearly completely absorbed from the gastrointestinal tract with very high bioavailability (from 85% to 90%) [3]. Serum concentration (SC) ranging from 0.2 to 1 mcg/ml provide the greatest therapeutic benefit but higher concentrations are associated with proarrhythmic side effects [4]. The apparent volume of distribution is wide, with only about 40% of drug bound to plasma proteins [5]. Flecainide is metabolized in the liver via cytochrome (CYP2D6 and CYP1A2) in meta-O-dealkylated flecainide (active, but about one-fifth as potent) and meta-O-dealkylated lactam (inactive form), then excreted in the urine. Since flecanide is mainly metabolized via cytochrome CYP2D6 [6], CYP2D6 inhibitors increase its plasmatic concentration and inductors decrease it. [7]. About 30% of an orally administered dose escapes liver metabolism and is excreted in the urine unchanged [3]. Elimination half-life is about 20 hours (range: 12-27 hours) [8], unaffected by dose, but it may be prolonged until 70 hours in patients with heart failure, renal disease (creatinine clearance < 50 ml/min) and liver disease [8] (**Table 1**).

Table 1. Pharmacokinetics properties of flecainide.

	Pharmacokinetics
Absorption	85-90% absorbed from the gastrointestinal tract; Serum concentration peak reached in 1-3 h.
Distribution	Wide volume of distribution; 40% binded to plasma proteins.
Metabolism	30% escapes liver metabolism.
Excretion	Excreted by urine; Elimination half-life: about 20 hours.

Pharmacodynamics

Flecainide works blocking the open-state fast inward Na+ channel Nav 1.5 [8] in a rate- and voltage-dependent manner, reducing the maximum rate of phase 0 rise of the action potential (Vmax) in fast channel-dependent myocardial fibers (mostly in His-Purkinje tissue and ventricular muscle, followed by atrial muscle) [9]. Moreover, flecainide at low dose inhibits rapid component of the delayed rectifier K+ current (IKr) [10] [11] while at higher concentrations inhibits other K+ channels (Kito) [12]. Flecainide exerts a variable effect in terms of action potential duration (APD) and effective refractory period (ERP) on ventricular fibers and the Purkinje fibers. In fact, while the ERP and APD in atrial and ventricular fibers are prolonged, in the Purkinje system are shortened [13]. This effect is probably consistent with Na^+ channel blockade [8][11][14]). Flecainide also inhibits ryanodine receptor 2 (RyR2) reducing calcium sparks [4] and arrhythmogenic calcium currents [15]. Moreover, flecainide reduces Na^+ and Ca^{2+} inflow in myocardial cells and exerts a negative inotropic effect. Intravenous administration reduces cardiac output and stroke volume [16][17]especially for patients with coronary artery disease [4][18][19][20] or left ventricular (LV) dysfunction [20] while has minimal hemodynamic effects in patients with normal, or nearly normal, ventricular function [4][8][21][22]

Furthermore, flecainide reduces atrial remodeling and oxidative stress by inhibiting intracellular Ca^{2+} accumulation. Indeed, atrial activation, when caused by atrial fibrillation, rapidly leads to intracellular calcium accumulation due to

Na^+/Ca^{2+} exchanger. This results in myocardial remodeling and mitochondrial dysfunction related to oxidative stress [23]

2. Vademecum for the Management of Flecainide

A 12-lead ECG is mandatory before starting the therapy with flecainide and after 1-2 weeks after its administration; symptomatic bradycardia, second degree or superior atrioventricular (AV) block, QRS duration longer than 120 ms or Brugada syndrome contraindicate the prescription of flecainide. [24] [7]

It is reasonable to perform an echocardiogram to evaluate LV function and exercise stress testing in high-risk patients to exclude the possibility of coronary artery disease. It is strongly suggested to test the first dose under medical observation. The minimum effective plasma concentration of flecainide is about 200 ng/mL while optimal range is between 200 ng/mL and 400 ng/mL [25]. This plasma concentration leads to a QRS prolongation of about 10 ms; a prolongation of 40 ms or more is associated to an increased probability of cardiovascular adverse effects [25]. A practical approach to flecainide dose ranging, in absence of kidney failure, is as follows [24] (see also—Figure 1):

1. Exclude contraindications (structural heart disease, symptomatic bradycardia, second degree or superior AV block, QRS > 120 ms or Brugada syndrome).
2. Record an ECG with a paper speed of 50 mm/sec and calculate the QRS duration (1 mm = 20 ms).
3. Administer a loading oral dose of 250 mg (200 mg if the weight is lower than 70 kg).
4. At plasma concentration peak, after 90–120 min, evaluate blood pressure and record an ECG with a paper speed of 50 mm/s and calculate the QRS duration.
5. Rule out Brugada ECG pattern and AV block.

- If the QRS duration is increased within 20 ms, prescribe 100 mg twice daily or 200 mg once daily. Check again the ECG after one week.
- If the QRS duration is increased between 20 and 40 ms or is wider than 120 ms, prescribe 50 mg twice daily or 100 mg once daily. Check again the ECG after 5 days.
- If the QRS duration is increased more than 40 ms or is wider than 130 ms, or a Brugada pattern is detected, consider flecainide contraindicated in that patient

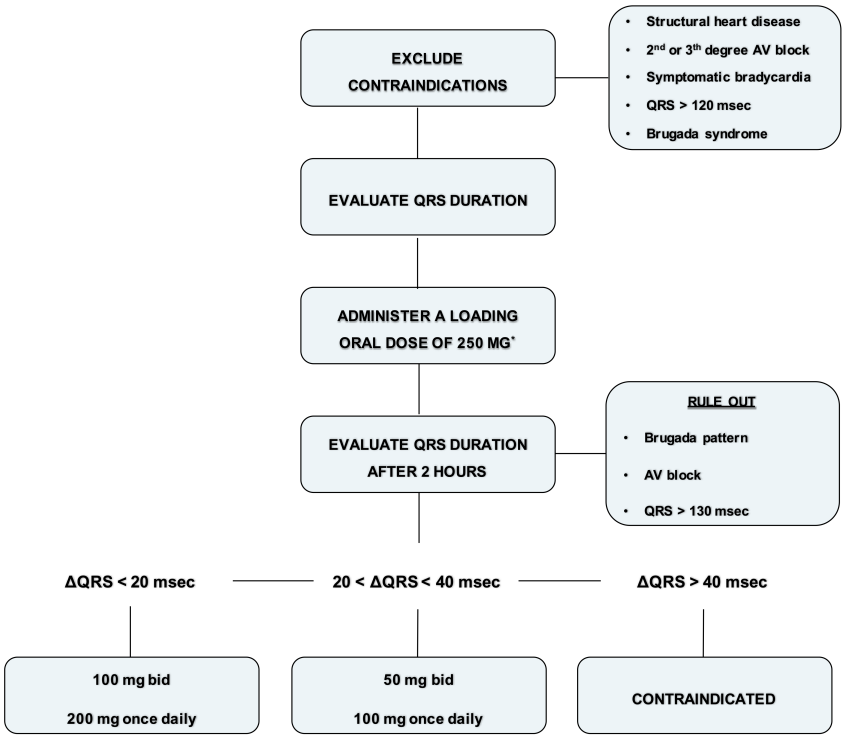

Figure 1. Flowchart for administration of flecainide. * Loading oral dose of 200 mg is recommended if the weight is lower than 70 kg.

There is a relationship between dose and concentration for both safety and efficacy. The incidence of adverse cardiovascular events rises with increasing flecainide plasma levels. However, the therapeutic effects, associated with greater than 90% suppression of premature ventricular beats (VPBs), are achieved at the range between 250–500 ng/mL of flecainide plasma levels. [25][26]. Clinicians should consider this aspect and adjust dosing according to the clinical response. [25]

Special Population

Periodic monitoring of flecainide plasma levels, blood pressure and ECG is required in patients with severe hepatic disease or severe renal failure. [25] [27]. Flecainide is predominantly excreted in the urine and the plasma elimination half-life is significantly prolonged in patients with renal impairment. [25][26][27]

Flecainide plasma levels and ECG monitoring are also indicated in elderly patients, who present decrease in renal function and an increased drug-drug interaction risk for the presence of comorbidities. [25] Furthermore, it has been demonstrated that there is an age-related decline of flecainide clearance in this population due to a CYP2D6 genotype. [6]

In pediatric patients a concentration of flecainide lower than the therapeutic concentration for adult patients is enough (concentration between 0.2 to 1 mcg/ml). [27]

3. Indication

Flecainide is an IC antiarrhythmic drug approved in 1984 from Food and Drug Administration for the suppression of sustained ventricular tachycardia and later for acute cardioversion of atrial fibrillation and for sinus rhythm maintenance [1]. Flecainide is used in paroxysmal supraventricular tachycardia (PSVT's), including atrioventricular nodal re-entrant tachycardia (AVNRT), AV re-entrant tachycardia (AVRT) and atrial fibrillation/atrial flutter in patients who do not have structural heart disease. Flecainide is also an option in treating life-threatening ventricular arrhythmias. The use of flecainide in atrial fibrillation represents the main indication of the drug.

3.1. Flecainide in Atrial Fibrillation

in converting recent onset of atrial fibrillation

Flecainide is very effective in restoring sinus rhythm in acute setting [28] with high percentages of success, greater than both propafenone and amiodarone [29] as well as with shorter cardioversion times (50% of patients are actually cardioverted in 1h if intravenous administration and in 3 h if orally given) [30][31][32][33][34][35]

Flecainide is effective even when administered orally at a charge dose ("pill in the pocket strategy"). The "pill in the pocket" strategy is currently indicated as a therapeutic strategy in selected patients (class IIa, level of evidence B), with recent onset of atrial fibrillation without significant structural or ischemic heart disease, but only following efficacy and safety assessment [7]

in long term rhythm control

Flecainide is currently recommended as a first-line long-term rhythm control in atrial fibrillation in class of recommendation I and level of evidence A, in patients with normal left ventricular function and without structural heart disease [7]

The maintenance of the sinus rhythm is more advantageous than rate-control both in terms of survival [36] and quality of life [37][38]. Several studies showed that flecainide is safe and effective in reducing the recurrences of paroxysmal AF and the time between episodes when compared to other antiarrhythmic drugs (table 2)

Table 2. Flecainide for maintenance of sinus rhythm.

Author	*n.* Patient	Type of AF	Compared Treatment	Endpoint of AF Recurrence	Results
Chimienti et al. [82]	200	Paroxysmal	Flecainide vs. Propafenone	Palpitation recurrence on days 15, 30, 90, 180, 270, 360	No difference between flecainide and propafenone
Gulizia et al. [83]	176 with PMK	Paroxysmal	Ic AAD vs. Amiodarone	Time to first occurrence of death, atrial cardioversion, cardiovascular hospitalization or change of AAD	IC AAD non inferior to Amiodarone. Similar AT recurrences
Naccarelli et al. [95]	239	Paroxysmal	Flecainide vs. Quinidine	AF recurrence at 12 months	Flecainide similar efficacy to quinidine but better tolerated

Allot et al. [94]	97	Paroxysmal	Flecainide vs. Propafenone	AF recurrence at 12 months	Flecainide similar efficacy to propafenone
Carunchio et al. [96]	66	Paroxysmal	Flecainide vs. Sotalolo vs. Placebo	AF recurrence at 1, 3, 6 and 12 months	Flecainide similar efficacy to sotalol and superior to placebo
van Wijk et al. [97]	26	Paroxysmal	Flecainide vs. Quinidine	AF recurrence during 3-months follow-up period	Flecainide superior to quinidine

AAD: antiarrhythmic drug, AF: atrial fibrillation; AT: atrial tachycardia; PMK: pacemaker.

Long term oral flecainide administration reduce the incidence of atrial fibrillation recurrence in patients with paroxysmal and persistent atrial fibrillation, extending the time between two episodes [39][40][41][42][43]. A large study conducted on 994 patients with paroxysmal atrial fibrillation (PAF) showed that, after 9 months of treatment with flecainide at the mean dose of 200 mg, 65% patients were free from arrhythmia [44].

Recently, a retrospective study involving 144 patients with atrial fibrillation demonstrated that flecainide is effective and well tolerated, even at 12 months. After 6 and 12 months of treatment, 70.8% and 61.8% of patients respectively were symptomatically controlled [45].

3.2. Flecainide in Supraventricular Tachyarrhythmias

Flecainide is recommended for focal atrial tachycardia (if other treatment failed), in atrial flutter, in atrioventricular nodal re-entrant tachycardia (AVNRT) and atrioventricular re-entrant tachycardia (AVRT). In pregnant women should be considered for prevention of supraventricular tachycardia (SVT) in patients with Wolff–Parkinson–White (WPW) syndrome and without ischemic or structural heart disease. [46]

Flecainide reduces the recurrences of supraventricular arrhythmias, and this could be related to the inhibition of the potassium and calcium currents with consecutive reduction of cellular excitability. Usually, betablockers are used as a first line therapy in atrioventricular nodal re-entry tachycardia, but flecainide represents an alternative if beta-blockers are not effective or contraindicated. [27]

3.3. Flecainide in Ventricular Tachycardias

The treatment of ventricular tachycardia represented the first historical clinical indication for flecainide [27] [47]

Usually, ventricular tachycardias with a low heart rate are provoked by very slow conduction isthmuses and, on areas already characterized by very slow conduction velocity, flecainide is effective. [48]

Flecainide plays a key role in management of Premature Ventricular Complexes (PVC) and of Ventricular Tachycardia (VT) in structurally normal hearts with a class I indication and should be utilized as first line therapy in these patients beside radiofrequency ablation. Choice between drug therapy and ablation is based on patient choice and procedure complexity and risks.

Flecainide may be useful as add-on therapy in management of some rare channelopathies such as Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) and some subtypes of long QT syndrome, LQTS type 3 and Andersen – Tawil Syndrome (LQTS type 7). [49]

Flecainide is very effective in CPVT which usually has a high frequency. In this arrhythmia, however, the efficacy seems to be related to a different mechanism of action. CPVT is induced by calcium overload due to sympathetic activation and to a diastolic calcium release from the sarcoplasmic reticulum through defective leaking RYR2 channels. Flecainide blocks the RYR2 channels allowing direct targeting of the molecular defect [50].

Flecainide is effective in patients with Long QT Syndrome (LQT) type 3 as it inhibits not only the peak but also the late component of the sodium current, inducing an abbreviation of the QT interval. This form, indeed, is provoked by mutations that increase the late sodium current [51]

3.4. Flecainide in Association with Other Antiarrhythmic Drugs

In some AF patients may be difficult to maintain sinus rhythm and symptomatic AF episodes remains a difficult therapeutic problem. Therefore, a combined anti-arrhythmic strategy may be necessary in some cases. Flecainide combination with amiodarone is interesting, not only because it may be effective when the efficacy of each is inadequate as a single-drug therapy, but also because it is relatively safe and may allow a reduction in their respective dosages and side effects [52] [53][54]

Beta blockers are the most used antiarrhythmic drug in association with flecainide. Capucci and colleagues have demonstrated that combination therapy with flecainide and metoprolol significantly reduced recurrences at 1-year follow-up when compared with flecainide alone in the whole population and in patients with persistent AF, while in patients with paroxysmal AF no benefit was observed over IC anti-arrhythmic drug-only. [55]

The association of flecainide with other AV blockers as digoxin is frequent; close monitoring of serum digoxin concentrations is recommended because it could increase 6 hours after co-administration with flecainide by 15–19% [56][57]

In the same way, it is necessary to consider with caution the combination of flecainide with verapamil, because of potential additive effects on myocardial contractility and on atrioventricular conduction [57]

3.5. Contraindications

According to 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation, flecainide is contraindicated in patients with ischemic heart disease and/or significant structural heart disease. Flecainide may induce hypotension and mild QRS complex widening. Furthermore, may increase atrial flutter cycle length, thus promoting 1:1 atrioventricular conduction and increasing ventricular rate; this risk can be reduced by concomitant administration of an atrioventricular nodal blocking drug such as a beta-blocker or non-dihydropyridinecalcium-channel blocker[7]

A practical guide on the management of adverse events due to flecainide is provided in Table 3.

Table 3. Management of adverse events due to flecainide.

Adverse Event	Incidence	Indication
Drug induced Brugada	<1%	Discontinue
QRS increased more than 40 ms or wider than 130 ms	<1%	Discontinue
QRS increased more than 20 ms	1–2%	Reduce Dosage
Bradyarrhythmia, sinus pause, AV block	1–2%	Discontinue
Hypotension	3–5% (mostly with IV)	Reduce Dosage
1:1 atrial flutter	3–5%	Discontinue and consider ablate CTI dependent-flutter
Worsening heart failure	<1%	Discontinue
Extracardiac effects (dizziness, tremor, nausea)	1–2%	Reduce Dosage

AV: atrioventricular; CTI: cavotricuspid isthmus; IV: intravenous.

4. Controlled release flecainide

The controlled-release (CR) formulation of flecainide acetate allows once-a-day administration therapy. The pharmacokinetic profile is characterized by a reduced and delayed reaching maximum concentration (Cmax) and lower fluctuations of plasma concentrations during a dosing interval compared with immediate-release form. Serum concentration peak of slow-release form is reached in 26 h, the steady state plasma level is reached after 4-5 days ranging from 270 to 330 ng/ml far from plasma level at risk of side effects [58]. After repeated-dose administration,

maximum and minimum QRS prolongation does not differ between the two forms but with the CR-formulation there is a less variability compared with the immediate-release form [58]. Moreover, CR formulation improves treatment compliance and, reducing variability and peaks, decreases the risk of side effects and interactions with other drugs, preserving clinical benefit. Controlled-release flecainide is also effective in long-term prevention of atrial fibrillation recurrences. In 227 outpatients with paroxysmal atrial fibrillation and treated for 24 weeks with controlled-release flecainide at the dose of 200 mg, there was a decrease of incidence of paroxysmal atrial fibrillation episodes from 28.6% at baseline to 11% at the end of the study ($p<0.0001$) recording by Holter [59].

Recently, in a prospective multicenter observational study that enrolled 679 patients with paroxysmal and persistent atrial fibrillation, was reported that a treatment with flecainide at controlled-release form improve quality of life and have a good safety profile. Indeed, the treatment with CR flecainide reduced the CCS-SAF score from 1.64 at baseline to 1.32 at the end of the study ($p < 0.0001$) and only the 0,6% of patients experienced non serious adverse events (dizziness, presyncope, flushing and a new-onset left bundle branch block). Furthermore, the compliance to treatment with flecainide at controlled-release form was elevated during 12-weeks period (100% in 93,6% of patients). This high compliance may reflect the once daily dosing regimen and this trend has a considerable impact on cardiovascular disease medications [60].

Moreover, patients in treatment with flecainde immediate release form could be switched to the controlled-release formulation on a “mg-for-mg” daily dose basis, without any special need to monitor serum level. Harrison and colleagues demonstrated that all the subject in treatment with immediate release form of flecainide were successfully switched to the controlled-release form with this approach. [61]

5. Conclusions

Flecainide, administered bis in die (immediate-release form) or once daily (controlled-release form), is effective for the acute termination and for the chronic suppression of atrial fibrillation and ventricular arrhythmia. An excellent safety profile is described in patients with minimal or no signs of structural heart disease while mounting promising evidence will be available in patient with cardiomyopathy. A 12-lead ECG is required before starting therapy while ECG monitoring is suggested in case of drug adjustments or concomitant therapy with other antiarrhythmic drugs, particularly in the elderly and in patients with hepatic and/or renal dysfunction.

Despite the evidence supporting the efficacy and tolerability profile of flecainide, it is still underused due to the wrong idea about the risk for ventricular proarrhythmia. This aspect is even more clear with the controlled release form.

The immediate-release form (IR) and controlled-release form (CR) of flecainide have the same pharmacokinetic properties (absorption, distribution and excretion), but the pharmacokinetic profile of CR flecainide is characterized by a reduced and delayed reaching maximum concentration (Cmax) and lower fluctuations of plasma concentrations during a dosing interval compared with immediate-release form. Controlled release formulation

improves treatment compliance and, reducing variability and peaks, decreases the risk of side effects and interactions with other drugs preserving clinical benefit.

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