Flecainide, It is officially back

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Flecainide

- Is a class 1C antiarrhythmic (Na channel blocker) with half life 12-27hrs, metabolized in liver and mostly excreted from urine.
- Orally administrated flecainide is administrated twice daily and is absorbed rapidly without any significant interactions with food or antacid.
- Its bioavailability is around 90%, indicating no significant first pass effect through the liver. In normal subjects, plasma peak levels are reached after 2-3 h and steady state levels within 3-5 d.
- Flecinide 100 mg was first registered in Germany in June 1982.

Flecainide

- The original indication was for ventricular arrhythmias after which was extended to supraventricular arrhyhtmias.
- In 1989 flecainide was withdrawn from the CAST trial due to higher mortality rate in the arm of flrecainide or ecainide against placepo in post MI patients.

- The publication of the Cardiac Arrhythmia Suppression Trial (CAST) study in 1989, which was designed to investigate the efficacy of class I antiarrhythmic agents encainide or flecainide in patients after myocardial infarction with reduced ejection fraction and frequent ventricular ectopic beats, resulted in a major revision of the role of these antiarrhythmic drugs.
- Thus, while flecainide suppressed ventricular ectopy in those patients, a threefold increase of arrhythmic death was recorded compared to placebo.

- Based on CAST results, flecainide nowadays is not recommended for patients with structural heart disease and coronary artery disease.
- However, it is recommended as one of the first line therapies for pharmacological conversion as well as maintenance of sinus rhythm in patients with atrial fibrillation and/or supraventricular tachycardias without structural heart disease.

Clinical safety

- In general, class 1C AADs are associated with specific risk factors for proarrhythmic events.
- The results of CAST raised important issues regarding the safety of AADs to suppress arrhythmias or prevent arrhythmia recurrences.

Clinical safety

- When used in appropriately selected patients, flecainide has shown a good safety profile, as demonstrated by more than 25 years' of cumulative experience with the drug throughout the Europe and the USA.
- A recent systematic review determined the incidence of ventricular arrhythmias in flecainide-treated patients to be <3%.*

*McNamara RL, Tamariz LJ, Segal JB, Bass EB. Management of atrial fibrillation: review of the evidence for the role of pharmacologic therapy, electrical cardioversion, and echocardiography. An Intern Med 2003; 139: 1018-1033

Clinical safety

- A meta-analysis of 122 flecainide studies included 4811 patients with supraventricular arrhythmias but no significant signs of ventricular damage, with a mean exposure time of 241 ± 224 days. Compared with controls, flecainide was associated with a lower incidence of proarrhythmic episodes (2.7 vs. 4.8%), angina symptoms (1 vs. 1.3%), hypotension (0.8 vs. 1.3%), diarrhoea (0.7 vs. 2.8%), headache (2.0 vs. 2.9%), and nausea (1.6 vs. 1.8%). *

*Wehling M. Meta-analysis of flecainide safety in patients with supraventricular arrhythmias. Arzneimittelforschung 2002;52:507-14.

Clinical safety

- Mortality attributable to flecainide in the meta-analysis was lower than expected in the general population (total mortality: 0.166%; mortality rate per 100 patient years: 0.397).

Clinical efficacy

- Flecainide is highly effective in the acute setting for cardioversion of AF. In haemodynamically stable patients with acute-onset AF (<48 h duration) and preserved LV function, flecainide restores SR in up to 95% of patients within 1h from the start of the infusion. *

- *McNamara RL, Bass EB, Miller MR, Segal JB, Goodman SN, Kim NL et al. Management of new onset atrial fibrillation. Evid Rep Technol Assess (Summ) 2000:1-7

- A further single-blind, randomized, comparative study showed that SR was achieved in 90% of patients treated with flecainide (2 mg/kg bolus, plus second bolus of 1 mg/kg if the first dose did not convert), compared with 72% of patients treated with propafenone and 64% of patients treated with amiodarone (P = 0.008).*

*Martinez-Marcos FJ, Garcia-Garmendia JL, Ortega-Carpio A, Fernandez-Gomez JM, Santos JM, Camacho C. Comparison of intravenous flecainide, propafenone, and amiodarone for conversion of acute atrial fibrillation to sinus rhythm. Am J Cardiol 2000;86:950-3.

Clinical Efficacy

- Although patients may also spontaneously convert to SR, this usually takes much longer than with active iv drug. Indeed, flecainide significantly foreshortens conversion to SR. Both iv and oral flecainide can, therefore, play important roles in shortening the periods of symptomatic AF, thereby limiting complaints.

- Several randomized controlled clinical trials have also compared the efficacy of flecainide to other antiarrhythmic agents in acute conversion of recent onset atrial fibrillation.
- Capucci et al found that a single oral loading dose of flecainide was significantly more efficient than intravenous amiodarone within 8 h but not at 24 h.

- Martínez-Marcos et al found that a significantly higher proportion of patients reverted to sinus rhythm when treated with intravenous flecainide as compared to intravenous amiodarone and propafenone, although the difference in reversion rate with intravenous propafenone reached statistical significance at 12 h but not at 8 h following treatment onset.

- On the other hand, Romano et al found a significantly higher efficacy of intravenous flecainide compared to intravenous propafenone in acute conversion of recent onset atrial fibrillation at 1, 3 and 6 h, although no difference was evident at 24 h.
- Boriani et al evaluated the conversion efficacy of different antiarrhythmic drug protocols and reported that oral flecainide had a similar conversion rate to oral propafenone.

The Flec-SL trial

- The Flec-SL trial is the largest, prospective randomized clinical trial testing the efficacy of oral antiarrhythmic treatment for prevention of atrial fibrillation recurrence, with a meticulous follow-up and endpoint assessment.

- The aim of the study was to evaluate whether short-term (4 wk) flecainide treatment is non-inferior to long-term (6 mo) treatment following cardioversion of persistent atrial fibrillation.

- In total, 635 patients were randomly assigned in three treatment arms (placebo vs short-term vs long-term oral flecainide treatment).
- Patients were followed up for 6 mo with daily telemetric electrocardiograph recordings and Holter ECGs when atrial fibrillation was noted in more than two consecutive telemetric recordings.

- The primary outcome measure of the study was time to first recurrence of persistent atrial fibrillation or death from any cause.

- Based on the study results, in the per-protocol population 46% of patients receiving short-term treatment presented a recurrence of persistent AF as compared to 39% in the long-term treatment group.
- Additionally, short term treatment with flecainide was superior to placebo but failed to demonstrate non-inferiority as compared to long-term treatment.

- However, short term treatment demonstrated about 80% of the 6-mo effect of long-term treatment, supporting that the former could be considered a viable treatment option in patients with infrequent AF recurrences or increased risk of proarrhythmia.

Clinical Efficacy

- Flecainide is also a safe and effective agent for termination of AF in patients with Wolff-Parkinson-White (WPW) syndrome. Classically, iv procainamide is suggested as the first-line drug,but this is less effective in terminating AF.
- By reducing the safety of conduction over the accessory pathway, flecainide blocks conduction and slows the ventricular rate. Flecainide infusion during AF in WPW patients is therefore extremely safe. In addition to rate slowing, flecainide eventually converts AF to SR.*

*Fuster V, Ryden LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA et al. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: full text: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 guidelines for the management of patients with atrial fibrillation) developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. Europace 2006;8:651-745.

Precautions

- No serious adverse events were reported when patients were ECG monitored and in a resting condition.
- Atrial flutter with 1:1 conduction (producing fast ventricular rates) can occur immediately before conversion with a rate of 0.2%, particularly during exercise.
- A long asystolic pause may also occur at the time of conversion. These constitute the main reasons for administering the first loading oral dose under strict ECG and clinical control in a hospital setting.

'pill-in-the-pocket'

This, so-called, 'pill-in-the-pocket' approach has become a means of treating patients with paroxysmal or persistent symptomatic AF with an average ventricular rate of 70/min or greater.

However, this strategy is only suitable for selected patients; the episode has to be of recent onset (within 48 h) in a patient with normal QRS duration and of good LV function, without SA or AV nodal dysfunction, bundle branch block, structural cardiomyopathy or Brugada syndrome.

Maintenance of Sinus Rhythm

- Maintenance of Sinus Rhythm In PAF, flecainide has been shown to significantly reduce the number of AF recurrences, and lengthen the time between episodes.
- A meta-analysis of 60 studies with flecainide showed that 65% of patients were responsive to treatment in the short-term, and 49% in the long-term, indicating that the clinical benefit of flecainide for maintaining SR is sustained.*

*Hohnloser SH, Zabel M. Short- and long-term efficacy and safety of flecainide acetate for supraventricular arrhythmias. Am J Cardiol 1992;70:3A-9A; discussion A-10A.

- Flecainide also reduces the symptoms associated with AF; significantly more patients receiving flecainide reported suppression of palpitations ($P < 0.001$), tachycardia ($P = 0.027$), and chest pain ($P = 0.023$), compared with those receiving placebo.*

*Anderson JL, Gilbert EM, Alpert BL, Henthorn RW,Waldo AL, Bhandari AK et al. Prevention of symptomatic recurrences of paroxysmal atrial fibrillation in patients initially tolerating antiarrhythmic therapy. A multicenter, double-blind, crossover study of flecainide and placebo with transtelephonic monitoring. Flecainide Supraventricular Tachycardia Study Group. Circulation 1989;80:1557-70.

Flecainide and AF
2014 ACC guidelines

5.3. Pharmacological Cardioversion

CLASS I

1. Flecainide, dofetilide, propafenone, and intravenous ibutilide are useful for pharmacological cardioversion of AF or atrial flutter, provided contraindications to the selected drug are absent (120-125). *(Level of Evidence: A)*

2. Propafenone or flecainide ("pill-in-the-pocket") in addition to a beta blocker or nondihydropyridine calcium channel antagonist is reasonable to terminate AF outside the hospital once this treatment has been observed to be safe in a monitored setting for selected patients (120). *(Level of Evidence: B)*

2. The following antiarrhythmic drugs are recommended in patients with AF to maintain sinus rhythm, depending on underlying heart disease and comorbidities *(Level of Evidence: A)*:

   a. Amiodarone (129-132)

   b. Dofetilide (124,128)

   c. Dronedarone (133-135)

   d. Flecainide (130,136)

   e. Propafenone (130,137-140)

   f. Sotalol (130,138,141)

2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS

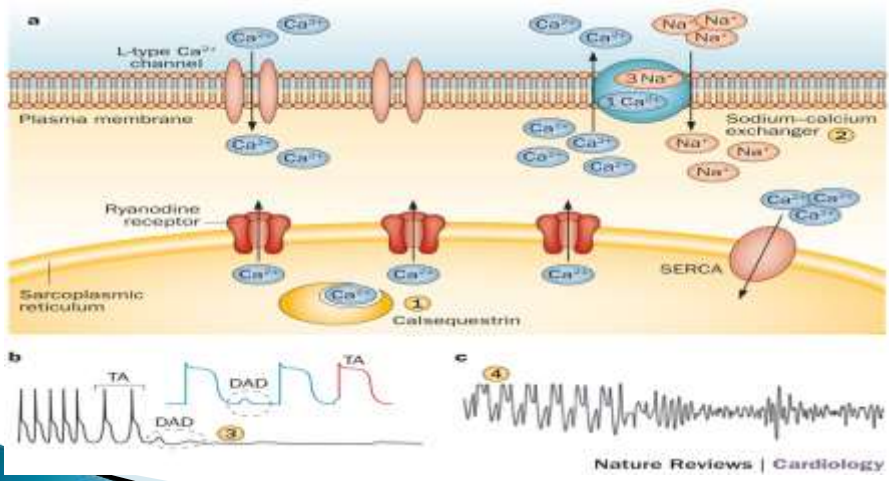
- Felcainide is also present as a class I indication for cardioversion of atrial fibrillation, maintenance of sinus rhythm post cardioversion and as one of the drugs to be used in the pill in pocket strategy

Contraindications to flecainide

- When using felcainide we have to make sure non of the following is present;

- Sinus or AV node dysfunction
- Heart failure
- Coronary artery disease
- Atrial flutter
- Brugada syndrome
- Liver or renal disease.

Flecainide and CPVT



Flecainide and CPVT

- Flecainide exerts a negative inotropic effect that may relate to reduced Na+ entry with subsequent reduced Ca2+ entry into the myocardial cells. In addition, it blocks the intracellular interaction between Ca2+ and the ryanodine receptor.
- Accumulating data have verified that flecainide inhibits the cardiac ryanodine receptor open state, thus directly targeting the molecular defect responsible for diastolic calcium release, delayed afterdepolarizations, and triggered arrhythmias in CPVT.

Summary

- Flecainide is always recommended as first line treatment in various arrhythmias in patient without structure heart disease.
- Flecainide is highly effective in cardioversion of acute AF.
- Flecainide is verey effective in af rhyhtm control.
- Is a safe drug well tolerated


Thank you