Proarrhythmic Effects Of Antiarrhythmic Drugs: Case Study Of Flecainide Induced Ventricular Arrhythmias During Treatment Of Atrial Fibrillation

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Abstract

Purpose : Flecainide is a class 1C antiarrhythmic drug especially used for the management of supraventricular arrhythmia. Flecainide also has a recognized proarrhythmic effect in patients treated for ventricular tachycardia. It is used to treat a variety of cardiac arrhythmias including paroxysmal atrial fibrillation, paroxysmal supraventricular tachycardia and ventricular tachycardia. Flecainide has local anesthetic effects and belongs to the class 1C AADs that block sodium channels, thereby slowing conduction through the heart. It selectively increases anterograde and retrograde accessory pathway refractoriness. The action of flecainide in the heart prolongs the PR interval and widens the QRS complex. The proarrhythmic effects however noted are not widely reported.

Method : We report a case of paroxysmal atrial fibrillation with structurally normal heart who was treated with oral Flecainide. There were no adverse events and no QTc prolongation was noted on ECG. Despite subjective improvement a repeat Holter detected him to have multiple short non sustained ventricular arrhythmias.

Results : Development of ventricular arrhythmias, salvos and non-sustained ventricular tachycardia after a month of initiation of oral flecainide detected by 24 hours ECG Holter lead to discontinuation of flecainide and subsequent early electrophysiological studies and successful ablation.

Conclusion : Initiation of oral Flecainide in a case of atrial fibrillation with subjective improvement and regular ECG monitoring, no QTc prolongation can still lead to development of dangerous ventricular arrhythmias. A cautious approach and thorough investigations and follow up are recommended.

Introduction

Flecainide is a class 1C antiarrhythmic drug used especially for the management of supraventricular arrhythmias such as paroxysmal atrial fibrillation (AF).[1] It causes rate- dependent slowing of the rapid sodium channel slowing phase 0 of depolarization and in high doses inhibits the slow calcium channel.[2] Flecainide also slows conduction in all cardiac fibers, increasing conduction times in the atria, ventricles, atrio-ventricular node and His-Purkinje system. Flecainide can also cause myocardial depression. In over- dose cases, flecainide can induce life treating ventricular arrhythmias and cardiogenic shock.

Case Report

Mr. RJN, 44 years male was diagnosed with paroxysmal atrial

Key Words:

Flecainide, Atrial Fibrillation, Ventricular Arrhythmias.

Disclosures:
None.

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fibrillation in May 2013 and was under beta blockers and acetyl salicylic acid. He was reviewed in our hospital in September 2013 because of his disturbing symptoms of palpitations and fatigue. Beta blockers were stopped and he was started with flecainide and dabigatran with the possibility of electrical cardioversion later if required. Regular follow ups were done and he reported subjective improvement starting after 3 days. Periodic ECG done did not show any QTc prolongation. He was reassessed with Holter after one month of flecainide treatment and found to have multiple short episodes of ventricular arrhythmias [salvos and non-sustained ventricular tachycardia] while still suffering from paroxysms of atrial fibrillation. Thereafter he was admitted to CCU and flecainide was stopped. He was switched back to beta blockers and again reassessed with Holter after a week which showed persistent atrial fibrillation with no ventricular tachyarrhythmia.

Risk Profile: No hypertension or diabetes. Nonsmoker.

Physical examination: Blood pressure: 110/70 mm of Hg, pulse rate: 102/minute irregular. No evidence of heart failure.

ECG: Initial: Atrial fibrillation, ventricular rate ~110/minute. On beta blockers currently.

With Flecainide: Paroxysmal AF with multiple nonsustained ventricular arrhythmias.

Fig 1   Holter trace showing Ventricular arrhythmias Fig 2 Holter

trace showing Ventricular arrhythmias

ECHO: Atrial fibrillation, normal LV dimensions and systolic function.

He underwent electrophysiological studies and successful isolation of all four pulmonary veins for paroxysmal atrial fibrillation with termination of focal site for AF initiation near mid/proximal coronary sinus roof.

Discussion

Pharmacological Treatment For Atrial Fibrillation

Pharmacological cardioversion of AF can be achieved using a number of drugs with different pharmacological properties, including disopyramide, procainamide, quinidine (all class IA), flecainide, propafenone (both class IC), dofetilide, ibutilide, sotalol, and amiodarone (all class III). Currently, the most commonly used drugs for chemical cardioversion are flecainide, sotalol, and amiodarone. Little difference is observed between the routes of administration for cardioversion rates, although intravenous administration results in faster conversion. Indeed, in patients with recent onset AF, successful cardioversion is reported in up to 80% of cases with oral therapy, rising only to 90% with intravenous administration.[1]

Unfortunately, recurrence of AF is common, often requiring long-term drug therapy to improve maintenance of sinus rhythm. For most current antiarrhythmic agents, the relapse rate is at least 50% during the first year,[2–5] although slightly better figures are seen with dofetilide[6] and amiodarone.[7, 8] A number of studies have also demonstrated that flecainide and propafenone are effective drugs for preventing AF recurrence.[9–11] The effectiveness of flecainide is comparable to quinidine, but with fewer side effects.[12] In contrast, propafenone is more effective for maintenance of sinus rhythm than quinidine. It is as effective as sotalol.[13, 14] Generally, however, class IC drugs are preferred to class IA drugs in view of their better safety profile.[12, 13] The success of electrical cardioversion for AF has been quoted as between 75 and 93%, although this depends on left atrial size and co-existing structural heart disease, and ultimately on the duration of AF.[15–17] Where there is some concern about a successful restoration of sinus rhythm (for example, previous cardioversion failure or early recurrence of AF), concomitant amiodarone or sotalol can be used pre-cardioversion to improve the success of electrical cardioversion.[18] Such an approach is advocated by the ACCF/AHA practice guidelines 2013 on AF management.[2] The frequency of recurrence of AF after electrical cardioversion is high, and maintenance therapy with antiarrhythmic drugs such as amiodarone or sometimes b-blockers is somewhat useful to prevent AF relapses.[1] Beta-blockers are very effective at controlling ventricular rate and also may reduce the risk of AF recurrence following successful cardioversion (whether spontaneous, pharmacological, or electrical) and are currently used as first-line prophylactic agents in paroxysmal AF. Rate-limiting, non-dihydropyridine calcium channel blockers (diltiazem, verapamil) are frequently used to optimize rate control where B-blockers are contraindicated or ineffective. A rate-limiting calcium antagonists (diltiazem, verapamil) are indicated where urgent pharmacological rate control is required. Intravenous amiodarone is a useful alternative in situations where the administration of b-blockers or calcium antagonists is not feasible, such as in the presence of heart failure. All current class IA, IC, and III antiarrhythmic drugs have significant side effects. This includes non-cardiovascular effects (e.g. pulmonary fibrosis and thyroid dysfunction with amiodarone), and
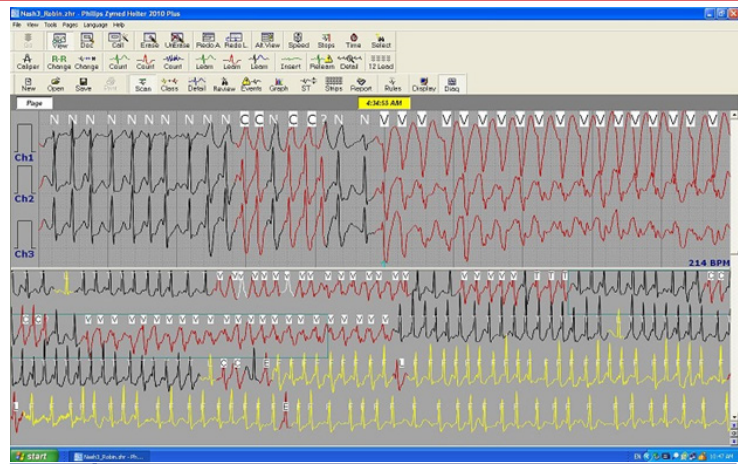

Figure 1:   Holter trace showing Ventricular arrhythmias

of particular importance, the risk of life-threatening ventricular proarrhythmia including TdP in up to 5% of patients.[19, 20] Most of these antiarrhythmic drugs prevent or terminate AF by altering the function of potassium or sodium channels within the atrial cells. Blockade of potassium channels may prolong ventricular repolarization — and hence, the refractory period — resulting in QT-interval prolongation. Given the risk of severe proarrhythmia, the safety profile of many current antiarrhythmic drugs is far from ideal.

From the early twentieth century, drug therapy has played an important role in the management of atrial arrhythmias. Quinidine was the first antiarrhythmic used to successfully restore and maintain sinus rhythm in atrial fibrillation (AF). Subsequently, a large number of other drugs have become available. Although the efficacy of many of these agents is impressive, side effects are a frequent occurrence. Amongst the most worrying side effects are QT-interval prolongation and risk of proarrhythmia, including torsade de pointes (TdP)[21]

Flecainide, a class 1C anti-arrhythmic agent, depresses the rate of depolarization of cardiac action potentials producing a membrane stabilizing action. It is a very effective anti-arrhythmic agent against supraventricular arrhythmias, nevertheless flecainide is contraindicated in patients with structural heart disease because it increased mortality.[22] The proarrhythmic effect of flecainide may be related to promoting a reentry in ventricular tissue. The phenomenon is due to a rate-dependent blockade of rapid sodium channels slowing phase 0 of depolarization and an inhibition of the slow calcium channel.[23] In cases of overdose, the mortality with class Ic agents has been reported to approach 22%. Conduction disturbances began with widening of QRS complex which can rapidly progress to ventricular tachycardia, electromechanical dissociation and asystole.

Despite the large number of available antiarrhythmic agents, significant QT-interval prolongation and risk of severe proarrhythmia, including torsade de pointes, limit pharmacological opportunities in the management of atrial arrhythmias. The risk of proarrhythmia has been demonstrated in class I and class III drugs, but significant variability has been observed between agents of the same class. Electrophysiological drug effects found to be important in the etiology of proarrhythmia include QT- interval prolongation through selective blockade of the delayed rectifying potassium current (IKr), early afterdepolarizations, transmural dispersion of repolarization, and a reverse rate dependence. Interestingly, less

proarrhythmic potential is seen or anticipated with agents that are able to block multiple ion channels and those with atrial selectivity, despite moderate QT prolongation. This observation has helped steer the development of newer drugs, with some promising preliminary results.

Conclusions

In conclusion, despite the large number of antiarrhythmic agents that are currently available, modern cardiology is still waiting for the introduction of new efficient and safe drugs for the treatment of atrial arrhythmias. The ideal anti- arrhythmic agent must efficiently cardiovert AF patients and prevent relapses without proarrhythmic potential. To achieve this, it seems that such drugs should be atrial selective, should have multi ion-channel effects, should not increase transmural dispersion of repolarization, should not produce early after depolarization, and should not exhibit reverse use-dependency.

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