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An electrocardiographic series of flecainide toxicity

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ABSTRACT

Anti-arrhythmic drugs (AADs) uniquely affect the various electrolyte channels in the heart and can slow conduction, increase refractoriness, and/or decrease automaticity with the goal of preventing tachyarrhythmias. Due to these properties, these same drugs are by nature pro-arrhythmic. Vaughan-Williams classification Ic AADs belong to a class of medications that inhibit sodium channels, leading to decreased conduction velocity of myocytes and Purkinje fibers as well as to decreased automaticity of pacemaker cells. When present in toxic amounts, this leads to classic changes on the electrocardiogram (ECG) that are harbingers of potentially lethal arrhythmias. Presented is a clinical series of ECGs that occurred in a patient who presented with flecainide toxicity.

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Abbreviations

AAD	Antiarrhythmic drug
AV	Atrioventricular
AF	Atrial fibrillation
ECG	Electrocardiogram

1. Introduction

Anti-arrhythmic drugs (AADs), like most medications, are toxins that, when used in the appropriate dose and clinical setting, are therapeutic. Sodium-channel blocking agents, using the Vaughan-Williams classification system, are known as Class I anti-arrhythmic drugs. Class Ic AADs, which include flecainide and propafenone, have both sodium channel (I_{Na}) and potassium-channel (I_{Kr}) blocking properties. In normal cardiac tissues, at therapeutic doses these medications slow depolarization and conduction, leading to QRS and QT prolongation (QT prolongation due to the widening of the QRS complex) [1]. When present in toxic amounts, there are various abnormal ECG findings that become apparent.

Flecainide toxicity can lead to bradycardia, sinoatrial block, and asystole, as well as to first and second degree atrioventricular block. Sinus bradycardia is more common in patients with pre-existing sinus node dysfunction [2]. Flecainide can also lead to conversion of atrial fibrillation to slow atrial flutter with one-to-one conduction [1]. Class Ic AADs, in general, are contraindicated in patients with ischemic heart disease and reduced ejection fraction due to an increased incidence of cardiovascular death which is believed to be secondary to arrhythmic events [3]. Early recognition of toxicity is important to prevent dangerous arrhythmias secondary to the properties of this medication. Presented is a series of ECGs demonstrating the ECG changes in serum doses of flecainide ranging from therapeutic to toxic. An overview of the underlying mechanism of these findings is also presented.

2. Case report

The patient is a 66-year-old woman with a history of symptomatic paroxysmal atrial fibrillation (AF), no known structural heart disease, and a previously normal stress test. Her AF was diagnosed two months prior when she presented with a right middle cerebral artery stroke. The patient's baseline ECG in sinus rhythm and the patient's initial ECG when the atrial fibrillation was diagnosed are shown in Fig. 1 and in Fig. 2, respectively. She was started on flecainide 100 mg twice a day and extended-release metoprolol succinate 25 mg daily, as well as apixaban 5 mg twice daily for systemic anticoagulation.

Additional past medical history includes a history of bladder

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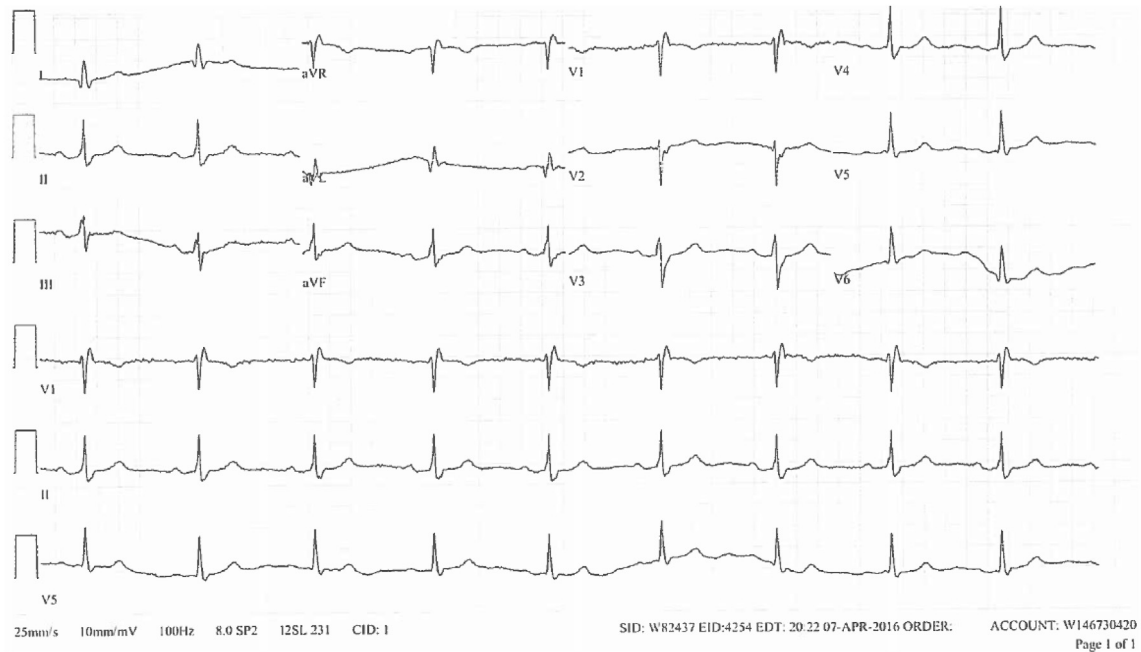


Fig. 1. Baseline ECG of patient prior to initiation of flecainide therapy.

cancer and of rheumatoid arthritis. The patient's clinical presentation with the new ECG findings was after two months of flecainide therapy. The ECGs on demonstrating the flecainide toxicity are shown in Fig. 3 and in Fig. 4 below. Four days prior to presentation, the patient had symptoms of fatigue and lightheadedness. Labs on presentation demonstrated mild acute renal failure with a creatinine increased to 1.35 mg/dL and potassium of 5.4 mEq/L. It is postulated that the acute renal failure led to flecainide toxicity. Cessation of flecainide resulted in complete resolution of the ECG changes.

3. Discussion

Flecainide was developed originally as a fluorinated anesthetic agent [4]. In animal and human models, it was found to suppress ventricular arrhythmias. Through further human studies in the 1980's, it was found to be effective in suppressing tachyarrhythmias secondary to accessory pathways and AV nodal reentry tachycardias [4]. Its mechanism of action is predominately through inactivation of fast sodium channels (I_{Na}), however it also has effects at lower

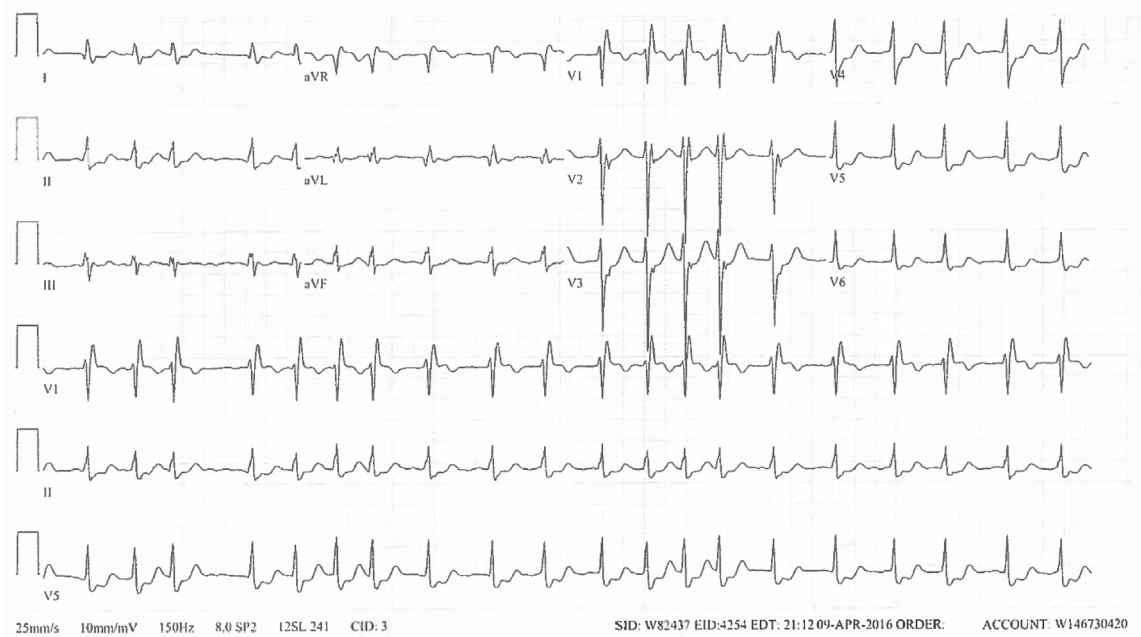


Fig. 2. Atrial fibrillation with rapid ventricular response.



Fig. 3. Sinus bradycardia, significantly widened QRS, 1st degree AV block.

doses on rapid inward rectifying potassium channels (I_{Kr}). Class 1c AADs have affinity for the I_{Na} channel in the open state and dissociate very slowly from the channel during the inactivated state. This results in use dependence, meaning that the drug has minimal effect at normal cardiac rates and increased effect in the setting of tachycardia [5]. The reduced influx of sodium intracellularly results in a reduced phase 0 slope and slowed conduction velocity. In addition, the mild effect on I_{Kr} can also lead to increased refractory periods of atrial, His-Purkinje, and ventricular cells via prolonged

action potential duration [5]. This is manifested on the ECG by a prolonged P-wave, prolonged QRS interval, and AV nodal block.

When the balance of slowed conduction and increased refractory period is skewed, the risk of reentry and proarrhythmia increases. Hence, the use of type 1c AADs is typically restricted to patients with a structurally normal heart. Many side effects of flecainide toxicity are more common in those with underlying cardiac dysfunction. This includes patients with sinus node dysfunction, His-Purkinje disease, and any history of ischemic heart disease with

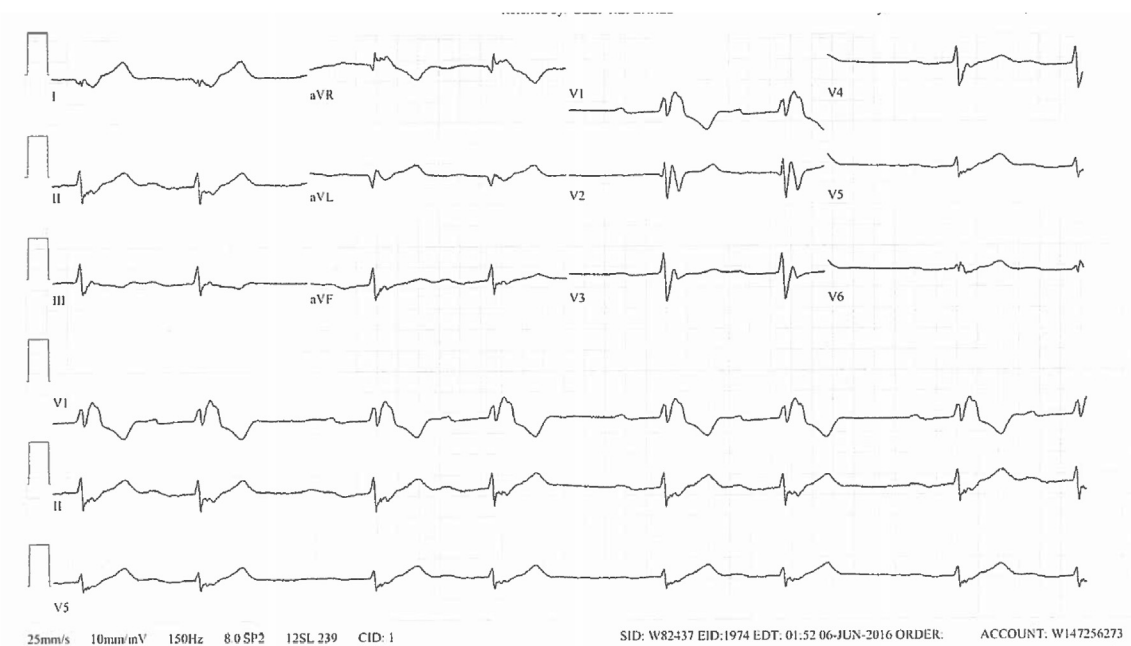


Fig. 4. Second degree type 1 SA block, significantly widened QRS, 1st degree AV block.

reduced ejection fraction or prior myocardial infarction.

Fig. 1 is the baseline ECG of the patient prior to the diagnosis of atrial fibrillation, demonstrating sinus rhythm with a 1st-degree AV block and a right bundle branch block. Fig. 2 is the presenting ECG in the Emergency Department when the atrial fibrillation was initially diagnosed. Fig. 3 shows the ECG on clinical presentation after two months of flecainide therapy, when she had symptoms of fatigue and lightheadedness. It demonstrates a markedly prolonged QRS duration of more than 160 ms, a marked first-degree AV block (a PR interval of 480ms), and sinus bradycardia at a rate of 42 beats per minute. The various degrees of AV block are secondary to the effect of flecainide on slowing conduction velocity in atrial, ventricular, and His-Purkinje tissues. The effect on the sinoatrial node likely reveals underlying sinus node dysfunction. Fig. 4 demonstrates second-degree type 1 sinoatrial block, a first-degree AV block, and a significantly widened QRS.

With discontinuation of flecainide and the normalization of renal function, her symptoms and the abnormal ECG findings

completely resolved.

Disclosures

None.

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