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Review Article

Flecainide-induced Failure to Capture: A Narrative Review

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Abstract:

Postoperative abdominal and visceral pain is a common complication in patients following appendectomy, especially when associated with peritonitis. The diaphragm, as the primary respiratory muscle innervated by the phrenic nerve (C3–C5), has extensive anatomical and functional relationships with thoracoabdominal and pelvic structures. Fascial restrictions or dysfunction in diaphragmatic movement may contribute to increased intra-abdominal tension and altered visceral mobility, thereby intensifying pain in the abdominal and pelvic regions. This case report presents a 45-year-old female patient who developed persistent abdominal and right thigh pain following an appendectomy complicated by peritonitis. The patient also suffered from right shoulder pain and was referred to physiotherapy for treatment of shoulder pain. In addition to standard physiotherapy, six sessions of diaphragmatic myofascial release were administered.

Outcomes measure were Pain that assessed using the Visual Analog Scale (VAS), chest expansion by tape measure, the Shoulder Pain and Disability Index by SPADI, and the satisfaction by SF-12 quality of life questionnaire. After six sessions treatment consists of diaphragmatic release besides of conventional treatment on shoulder, the patient reported a 90% reduction in visceral pain in the abdominal and inguinal areas. Chest expansion increased from 1.6 cm to 3.5 cm, and the SPADI score improved from 40 to 25. These findings suggest that restoring diaphragmatic mobility through myofascial release can significantly alleviate postoperative abdominal and referred pain, likely by reducing fascial tension and improving neurovisceral dynamics.

Key words: flecainide; pacemaker; dysfunction

Introduction

Flecainide is one of the most commonly used anti-arrhythmic drugs that can be prescribed to effectively treat supraventricular and ventricular arrhythmias. Many patients receive antiarrhythmic drugs while implanted with a Pacemaker. The Vaughan-Williams class Ic sodium-channel blocking agent, first synthetized in 1977, is used to convert and prevent episodes of AF with stable hemodynamics AV nodal reentry tachycardia and Wolff-Parkinson-White syndrome. The drug may also be indicated in the treatment of recurrence of dysrhythmias (e.g. idopathic ventricular tachycardias). It is contra-indicated in presence of ischemic heart disease, heart failure or LV dysfunction, left bundle branch block, bifascicular block or 2nd and 3rd degree AV block and sinus dysfunction. Clinical and electrocardiographic monitoring is required [1].

The antiarrhythmic effect of the drug is mediated by a rate-dependent slowing of the rapid sodium inward channel (NaV1.5) current (INa). This results in reduction of action potential duration (APD) by slowing the phase 0 of the AP in all cardiac tissues, but particularly the ventricular myocardium. Flecainide increasing atrial APD to a greater extent at faster rates may be due to sodium channel blockade resulting in decreased sodium loading and reduced Na+, K(+)-ATP'ase stimulation during tachycardia [2]. Flecainide has also been reported to reduce cardiac ryanodine receptor (RyR2)-mediated sarcoplasmic reticulum (SR) Ca^{2+} release. Effects of flecainide on RyR2 is complex, with different binding sites, mostly inhibiting calcium, thus modulating excitability. These caracteristics of flecainide are clinically useful in catecholaminergic polymorphic ventricular tachycardia (CPVT), associated with gain-of-function RyR2 mutations, but could contribute to occasional proarrhythmic phenomena [3].

The delay of electrical conduction in atria and ventricle, manifest on the ECG by a prolongation of the PR interval and QRS duration. QT interval prolongation is predominantly linked to QRS prolongation, while JT

interval is usually unchanged. Flecainide increases the AH interval (about 20%) and the HV interval (25%-50%), thus slightly slowing both intra-atrial and atrioventricular nodal conduction. Widening by 25% or more of the QRS interval as compared to the baseline value should lead to drug dosage decrease, as discontinuation is required in case of atrioventricular block, permanent complete bundle branch block, or sino-atrial block [4]. In some patients, high dose flecainide or class-Ic –AAD can trigger Brugada-like ECG patterns, so that it is used by electro-physiologists as diagnostic tool [5].

The described proarrhythmic effect of flecainide is explained by promoting re - entry in ventricular tissue. Recently, the description of paradoxical influence or activation on ryanodine receptor 2 under low activity conditions raised new potential explanations for pro-arythmic effect [6].

Normal functioning of a pacemaker depends on its ability to depolarize the myocardium leading to its contraction. The minimal energy required to induce myocardial depolarization and contraction is determined during a threshold measure. These depolarization thresholds are dynamic, depending of internal and external factors. Lead instability or micro-dislodgement, interface tissue oedema, inflammation, ischemia or hypoxia but also metabolic disorders as severe acidosis, ionic imbalances (hyperkalaemia) are known to raise stimulation thresholds. Chronic thresholds vary under physiological states. While sympathetic modulation like exercise and orthostatic posture can decrease stimulation threshold, vagal tone can increase threshold up to 30-40 % during digestion or sleep [7].

Certain drugs have been reported for decreasing stimulation thresholds such as sympathomimetic agents (epinephrine, ephedrine and isoproterenol) and corticosteroids [8]. These steroid's properties have been successfully used in now widely-spread steroid-eluting pacemaker leads to prevent usual inflammation-mediated threshold rise in early permanent lead implantation [9].

A number of drugs have been reported to raise stimulation thresholds. Beta-blockers or calcium-channel blockers have been suggested to raise capture thresholds, but clinical data have not confirmed significant variation [10].

If amiodarone can raise defibrillation threshold, the clinical influence on pacing threshold is not convincing [11].

While Class IA agents such a quinidine and procainamide may raise thresholds (but not defibrillation thresholds) at toxic levels or intravenously, Class IB agents (lidocaine, mexiletine) do not seem to have clinical effect on pacing threshold but on defibrillation thresholds at therapeutic levels. Cardiac glycoside digoxin, on the other hand, has been shown reducing pacing thresholds. Class-Ic-AAD are the anti-arrhythmic drugs that raise ventricular capture threshold the most at their upper therapeutic dose range [12].

In fact, more than encainide or propafenone, oral and intravenous flecainide have been shown to rise stimulation thresholds to up 520 % (160-200 % in average increase at chronic oral maximal dose of 400 mg per day), potentially leading to exit block and failure to capture ventricular myocardium, as demonstrated by Hellestrand. Ventricular escape rhythm depression in patients with atrio-ventricular block was also demonstrated [13].

Atrial thresholds were significantly elevated with propafenone potentially leading to atrial lead dysfunction [14].

Threshold increase is correlated to QRS-duration so that no threatening threshold rise (> 100% increase) is expected at less than 25 % QRS lengthening with propafenone treatment [15].

Furthermore, it has also been demonstrated that flecainide substantially raises defibrillation thresholds in open-chested pentobarbital anesthetized dogs [16].

The figures 1 and 2 display an intermittent failure to capture with activation delay and significantly major widened paced- QRS complexes in a case of subacute flecainide overdosis. Ventricular capture threshold increase is well known but still ECG displaying intermittent failure to capture is a rare finding [17-19].

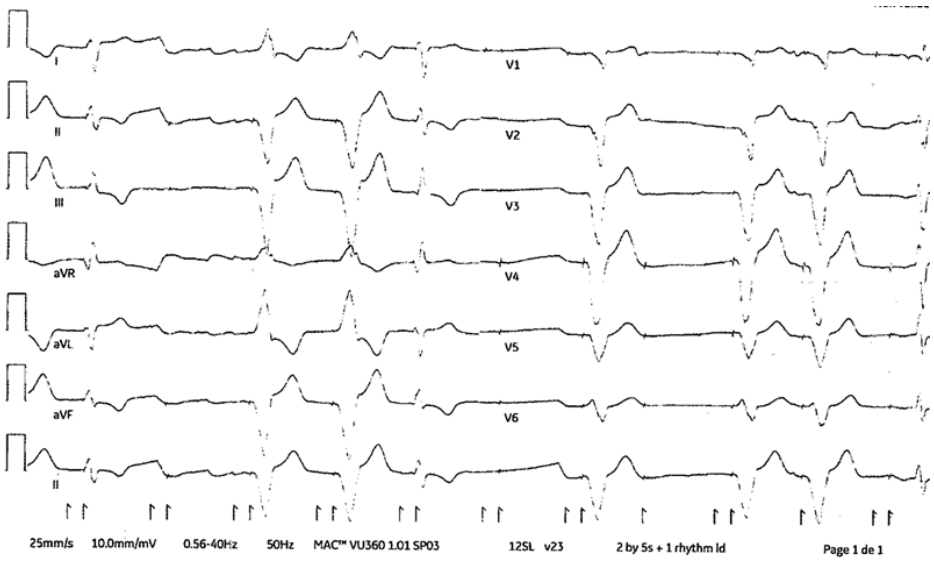

Figure 1: intermittent failure to capture with activation delay and significantly major widened paced- QRS complexes in a case of subacute flecainide overdosis

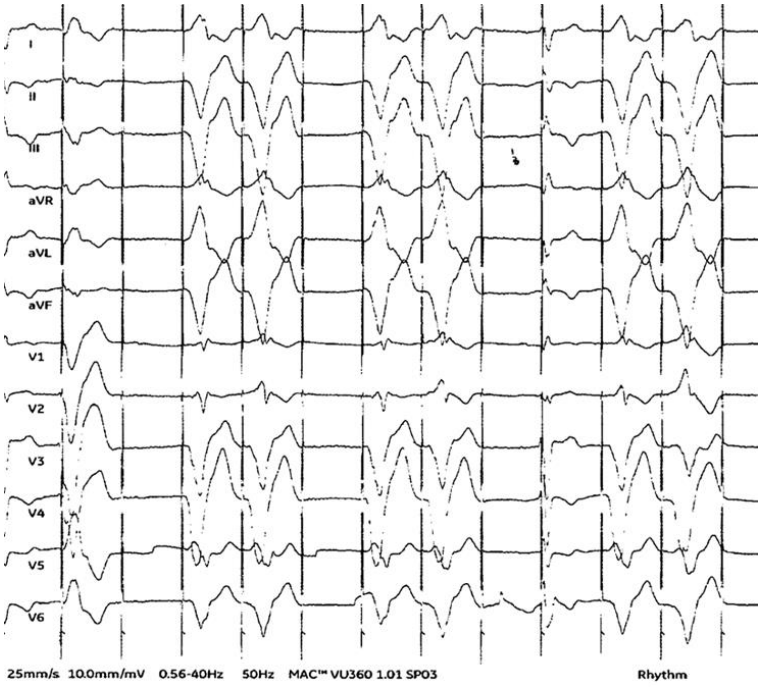

Figure 2: intermittent failure to capture: unipolar mode

Heart failure can be related to severe bradycardia and the drugs negative inotropic effect by reducing intracellular calcium concentration and interaction with Ryanodine-receptors [20].

Extreme caution should be taken in pacemaker-dependent patients, who do not have any intrinsic rhythm or whose intrinsic rhythm is suppressed by flecainide, as pacemaker dysfunction can lead to loss of consciousness, extreme bradycardia, heart failure and sudden death. Output adjustment and generous safety margins as well as automatic output regulation should be considered without neglecting medical monitoring in these patients.

In case of pacemaker dysfunction, a technical pacemaker issue such as lead displacement or rupture should be assessed by chest X-ray. First-line intervention consists of increasing the stimulation output of the device to assure persistent ventricular capture during drug clearance.

Flecainide clearance pathways are hepatic metabolization by cytochrome CYP 2D6 (to m-O- dealkylated flecainide, keeping 20 % of flecainide's initial antiarrhythmic effect, and other inactive metabolites), renal excretion of the molecule (up to 50 %) and its metabolites, while faecal excretion is marginal (5 %). Elimination half-life varies from 12 to 27 h in healthy individuals [21].

Simultaneous use of inducing drugs (antidepressants, neuroleptics, propranolol) or inhibitors (phenytoin, phenobarbital) of this iso-enzyme may respectively increase or decrease the plasma concentrations of flecainide. As the drugs clearance is globally moderately correlated to creatinine clearance, there is an important individual variability in serum drug levels due to hepatic oxidation enzyme polymorphism (sparteine/debrisoquin phenotype) so that renal function insufficiently predicts the drug's clearance [22-24]. EHRA guidelines recommend caution and dose reduction if GFR is below 50 mL/min/1.73 m2, while discontinuation is recommended below 35 mL/min/1.73 m2.

Nevertheless, the toxic effect of flecainide is transient and no remanent effect has been described. Flecainide can be administered orally or intravenously. In recent years, oral flecainide solution inhalation has been introduced for acute cardioversion of new-onset atrial fibrillation [25].

Drug overdose may occur in acute (suicide attempts) or chronic settings and may also include noncardiac manifestations, such as nausea, vomiting, dizziness, blurred vision and seizures [26]. The overall mortality with class 1c agents' overdoses has been reported to be as high as 22% [27]. This should underline the importance of diagnosis and intensive treatment.

Gastric lavage and activated charcoal administration should be undertaken in the early phase of large ingestion. Hypertonic sodium bicarbonate infusion in case flecainide toxicity is as well described first-line treatment (initial 50–100 mEq bolus with subsequent therapy targeting pH 7.5 and sodium concentration 150 mEq/L). Even if mechanisms aren't fully understood it has been shown that alkalization and sodium concentration increase reverse flecainide effects in animals, probably by decreasing Na-channel-receptor affinity to the molecule [28,29].

Calcium chloride or gluconate, amiodarone and lidocaine are to be considered in refractory arrythmias linked to flecainide intoxication but understanding of underlying mechanism and experience remain limited [30-32]. If transvenous pacing might be required in severe bradycardia, overdrive pacing may be ineffective in severe intoxications because of the rate-dependent properties of the molecule. Isoproterenol infusion has also been suggested for antiarrhythmic drug induced arrythmias and pacing capture failure [33]. Hyponatremia with normal flecainide serum level has been reported with similar pacemaker malfunction, as hyponatremia is thought to enhance the drugs toxicity [34].

Its lipophilic properties and high distribution volume make conventional dialysis or hemofiltration ineffective for clinically significant drug extraction but lipid-emulsion infusion [35] and hemo-adsorption technique (CytoSorb®) have been reported as therapies in severe flecainide intoxications.

Hemodynamic support by administration of beta-sympathomimetic agents may be needed and extra-corporeal life support (ECMO) might be required and in refractory shock or arrythmias [36,37].

Conclusion:

This review underscores the importance of recognising a particular pattern of pacemaker malfunction and the necessity of ECG and threshold monitoring with electrolyte control in patients treated with IC anti-arrhythmic drugs, especially those with advanced age and impaired renal function, including patients requiring stimulation devices and particularly the pacemaker-dependent patient.

Conflict of interest

The authors Declare no conflict of interest.

Consent

In terms of illustration, the Patient's consent was obtained prior to writing.

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