Effect of I_f Channel Blocker on Symptoms, quality of Life and Effort Tolerance in Patients with Idiopathic Dilated Cardiomyopathy

Thesis

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تأثير استخدام عقار الإيفا برادين على معدل بذل الجهد ومدى كفاءة الحياة

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Contents

List of Abbreviations

ACC	: American College of Cardiology
ACEI	: Angiotensin-Converting Enzyme Inhibitor
AHA	: American Heart Association
ARB	: Angiotensin receptor blocker
ARVC/D	: Arrhythmogenic Right Ventricular Cardiomyopathy/ Dysplasia
BB	: Beta-blocker
b.i.d	: twice daily.
Bpm	: beat per minute.
CIBIS II	: Cardiac Insufficiency Bisoprolol Study II
CRT	: Cardiac Resynchronization Therapy.
DBP	: Diastolic blood pressure.
DCM	: Dilated CardioMyopathy
DM	: Diabetes Mellitus
ECG	: Electrocardiogram.
ECHO	: Echocardiography.
ESC	: European Society of Cardiology
ET	: Endothelin.
HF	: Heart Failure.
HIV	: Human immunodeficiency virus
HR	: Heart rate
HRQL	: Health related quality of life
HTN	: Hypertension
IABP	: Intra Aortic Balloon Counterpulsation.

ICD	: Implantable Cardioverter-Defibrillator.
LVAD	: Left Ventricular Assist Device
LVEDD	: Left ventricular end-diastolic diameter
LVEDV	: Left ventricular end-diastolic volume
LVEF	: Left ventricular ejection fraction.
LVESD	: Left ventricular end-systolic diameter
LVESV	: Left ventricular end-systolic volume
MR	: Mitral regurgitation
NE	: Norepinephrine.
No.	: Number.
NS	: Non significant
NYHA	: New York Heart Association.
o.d.	: once daily.
PASP	: Pulmonary artery systolic pressure
PRO	: Patient related health outcome
RAS	: Renin-angiotensin system.
RV	: Right ventricle
SBP	: Systolic blood pressure
SD	: Standard Deviation.
SV	: Stroke Volume.
t.i.d	: three times a day.
VAD	: Ventricular Assist Device.
VT	: Ventricular Tachycardia.
WHO	: World Health Organization.

List of Tables

List of Figures

Introduction

Beta-adrenergic receptor blockers (BB) are strongly indicated in patients with myopathic ventricles, however a considerable percentage does not receive BB and this occurs for several reasons including absolute contraindications or intolerance to the recommended doses ***(Kannel et al., 1987).***

The benefits of beta-adrenergic receptor blockers in myopathic ventricles are multifactorial and are partly due to the gradual reduction in heart rate ***(Gullestad et al., 2001).***

The If channel blocker reduces the heart rate selectively without affecting the conduction system nor contractility by inhibiting the cardiac pacemaker f-current (If) ***(Vilaine et al., 2003).***

The If channel blocker has been approved to be effective as a beta-adrenergic receptor blockers alternative in ischemic heart disease without left ventricular dysfunction ***(Lars et al., 2005)***.

Data are also available for its use in ischemic heart disease with left ventricular dysfunction. But data for its use in left ventricular dysfunction without ischemic heart disease are still lacking.

Aim of the Study

The aim of the study is to prospectively assess the effect of If channel blocker on symptoms, quality of life and effort tolerance in patients with idiopathic dilated cardiomyopathy.

Dilated Cardiomyopathy

Definitions and Classifications of Cardiomyopathy:
Ongoing debate:

The concept of heart muscle diseases has a notable and evolving history. In the mid 1850s chronic myocarditis was the only recognized cause of heart muscle disease ***(Abelmann et al., 1984).***

In 1900, the designation of primary myocardial disease was introduced, and it was not until 1957 that the term cardio-myopathy was used for the first time. Over the subsequent 25 years, a number of definitions for cardiomyopathies were advanced in concert with an increasing awareness and understanding of these diseases. Cardiomyopathies, in the original 1980 WHO classification, were defined only as heart muscle disease of unknown cause reflecting a general lack of information available about causation and basic disease mechanisms ***(Bradenburg et al., 1980).***

The most recent WHO definition in 1995 was diseases of myocardium associated with cardiac dysfunction and included newly recognized arrhythmogenic right ventricular cardiomyopathy/ dysplasia (ARVC/D) and primary restrictive cardiomyopathy for the first time ***(Richardson et al., 1996).***

In 2006, AHA expert consensus panel proposed a novel definition: *Cardiomyopathies are a heterogeneous group of diseases of the myocardium associated with mechanical and/or electrical dysfunction that usually (but not invariably) exhibit inappropriate ventricular hypertrophy or dilatation and are due to a variety of causes that frequently are genetic*. Cardio-myopathies either are confined to the heart or are part of generalized systemic disorders, often leading to cardiovascular death or progressive heart failure-related disability ***(Maron et al., 2006).***

Within this broad definition, cardiomyopathies usually are associated with failure of myocardial performance, which may be mechanical (e.g, diastolic or systolic dysfunction) or a primary electrical disease prone to life–threatening arrhythmias. Indeed the ion channel opathies (long- QT syndrome [LQTS] and brugada syndrome among others) are primary electrical diseases without gross or histopathological abnormalities in which the functional and structural myocardial abnormalities responsible for arrhythmogenesis are at the molecular level in the cell membrane itself ***(Maron et al., 2006).***

In 2007, The European Society of Cardiology Working Group on Myocardial and pericardial Diseases proposed an update of the existing classification scheme defining cardio-

myopathy as a myocardial disorder in which the heart muscle is structurally and functionally abnormal, in the absence of coronary artery disease, hypertension, valvular disease and congenital heart disease sufficient to cause the observed myocardial abnormality ***(Elliot et al., 2008).***

Cardiomyopathies are grouped into specific morphological and functional phenotypes, each phenotype is then sub-classified into familial and non-familial. The most important principle underlying this proposed classification system is its relevance to everyday clinical practice. The division of cardiomyopathies into familial and non–Familial forms is designed to raise awareness of genetic disease as a cause of heart muscle dysfunction and to provide a logical framework on which to base further investigations ***(Elliot et al., 2008).***

Dilated Cardiomyopathy (DCM):

☒ Definition:

The WHO defined dilated cardiomyopathy as myocardial disease characterized by dilatation and impaired contraction of the left ventricle or both left and right ventricles. It may be idiopathic, familial/genetic, viral and/or immune, alcoholic/toxic, or associated with recognized cardiovascular disease in which the degree of myocardial dysfunction is not explained by the abnormal loading conditions or the extent of ischemic damage. The histologic

findings are frequently nonspecific. Presentation is usually with heart failure which is often progressive, arrhythmias, thrombo-embolism, and sudden death are common and may occur at any stage ***(Richardson et al., 1996).***

☒ Diagnostic criteria:

Mestroni et al. in ***1999*** identified the diagnostic criteria of dilated cardiomyopathy as left ventricular ejection fraction <0.45 (>2SD) and/or fractional shortening <25% (>2SD) as evaluated by echocardiography, radionuclide scanning or angiography and left ventricular end-diastolic diameter >117% of the predicted value corrected for age and body surface area, which corresponds to 2SD of the predicted normal limit +5%.These findings must be found in absence of:

1. Systemic arterial hypertension (>160/100 mmHg documented and confirmed at repeated measurements and/or evidence of target-organ disease).
2. Coronary heart disease (obstruction >50% of the diameter in a major branch).
3. History of chronic excess alcohol consumption, remission of heart failure after 6 months of abstinence.
4. Clinical, sustained and rapid supraventricular arrhythmias
5. Systemic diseases.
6. Pericardial diseases such as constrictive pericarditis.