Mexiletine versus Atenolol for The Treatment of Symptomatic Premature Ventricular Contractions

Thesis for partial fulfillment to master degree in cardiology

Submitted by **Hossam El-Din Ibrahim Abd El-Alim**M.B.B.CH.

UNDER SUPERVISION OF

PROF. MOHAMED KHIRY ABD EL-DAYEM

PROFESSOR OF CARDIOLGY AIN SHAMS UNIVERSITY

DR. OSAMA ALI DIABLECTURER OF CARDIOLOGY
AIN SHAMS UNIVERSITY

2011

مقارنة عقار المكسيليتين و الاتينولول لعلاج الانقباضات البطينية قبل الناضجةص

مقدم من الطبيب

د /حسام الدين ابر اهيم عبدالعليم

توطئة للحصول على درجة الماجستير في امراض القلب

تحت اشراف

أرد /محمد خيرى عبدالدايم أستاذ امراض القلب و الاعية الدموية جامعة عين شمس

د / اسامة على دياب مدرس امراض القلب و الاعية الدموية جامعة عين شمس 2011

Summary and Conclusion

Premature ventricular contractions (PVCs) are common and occur in a broad spectrum of the population. This includes patients without structural heart disease and those with any form of cardiac disease, independent of severity.

Ventricular premature beats produce few or no symptoms in the vast majority of patients, although occasional patients are incapacitated by palpitations or dizziness. PVCs rarely cause true hemodynamic compromise except in patients with frequent PVCs and severely depressed left ventricular function or when they are concurrent with a bradycardia.

This randomized clinical study included 50 patients with frequent symptomatic PVCs with no underlying cause, including 17 (34%) females and 33 (66%) males. The patients were selected as out-patients of national heart institute during the period between September 2007 and September 2009.

Patients with curable etiology for PVCs were excluded from the study.

LIST OF CONTENTS

Subject	Page
Introduction.	1
Aim of work	
Review:-	
Chapter 1: Prevalence and evaluation of premature ventricular contractions	5
Chapter 2: Clinical significance of premature ventricular contractions	25
Chapter 3: Treatment of Premature ventricular contractions	37
Chapter 4: Mexiletine: Pharmacology and clinical effects	43
Patient and methods.	59
Results	65
Discussion	82
Summary and conclusion	89
Master table	92
References	96
Arabic summary.	1

LIST OF Figures

Figure	Page
Figure (1): Percentage of symptom reduction after	71
treatment in both groups	
Figure (2): Median decrease in total number of PVCs	72
after treatment in both groups	
Figure (3): Median decrease in percentage of PVCs to	
total recorded beats after treatment in both groups	
Figure (4-A): 24 h Holter sample before mexiletine	74
therapy (case no. 5, group I)	
Figure (4-B): 24 h Holter sample after mexiletine	75
therapy (case no. 5, group I	
Figure (5-A): 24 h Holter sample before mexiletine	76
therapy (case no. 11, group I)	
Figure (5-B): 24 h Holter sample after mexiletine	77
therapy (case no. 11, group I)	
Figure (6-A): 24 h Holter sample before atenolol therapy	
(case no. 20, group II)	
Figure (6-B): 24 h Holter sample after atenolol therapy	79
(case no. 20, group II)	
Figure (7-A): 24 h Holter sample before atenolol therapy	80
(case no. 22, group II)	
Figure (7-B): 24 h Holter sample after atenolol therapy	
(case no. 22, group II)	

ص0.

LIST OF Tables

Table	Page
Table (1): Baseline characteristics of the study groups	66
Table (2): Group I (mexiletine group) before and one week after treatment	69
Table (3): Group II (atenolol group) before and one week after treatment	70

LIST OF Abbreviations

%.	percentage
ACC	American College of Cardiology
AHA	American Heart Association
ARIC	Atherosclerosis Risk in Communities
AV node	Atrioventricular node
AVN	Atrioventricular node
BHAT	Beta Blocker Heart Attack Trial
Bpm	beat per minute
CAMIAT	Canadian Amiodarone Myocardial
	Infarction Trial
CAPS	Cardiac Arrhythmia Pilot Study
CHD	coronary heart disease
CHF-STAT	Survival Trial of Antiarrhythmic
	Therapy in Congestive Heart Failure
DOC	drug of choice
ECG	Electrocardiography
Eg	example
EMIAT	European Myocardial Infarct
Trial	Amiodarone
EP	electrophysiology
ESC	European Society of Cardiology
ESVEM	electrophysiologic study versus
	electrocardiographic monitoring trial
FEV1	forced expiratory volume in one
HF	heart failure
HR	heart rate
IV	intravenous
LVEF	left ventricular ejection fraction

List of Appreciations

LVH	left ventricular hypertrophy
Mg/kg	milligram per killiogram
Mg/min	milligram per minute
MI	myocardial infarction
MRFIT	Multiple Risk Factor Intervention Trial
Msec	millisecond
No.	number
NSVT	nonsustained ventricular achycardia
P2	Pulmonary component
PACs	premature atrial contractions
PVCs	premature ventricular contractions
S2	second heart sound
SCD	sudden cardiac death.
VC	vital capacity
VES	ventricular extrasystoles
VPBs	Ventricular premature beats
VPCs	ventricular premature complexes
VPDs	Ventricularpremat ure depolarizations
VT	Ventricular tachycardia

Introduction

Premature ventricular contractions (PVCs) are the most common arrhythmias observed in the absence of heart disease. They have been described in 1% of clinically normal people as detected by standard ECG and 40–75% of apparently healthy persons as detected by 24-48 h Holter recording (*André et al* 2006)

Frequent PVCs (>60/h or 1/min) and complex PVCs occur in 1-4% of the general population and are generally of benign prognosis in the absence of heart disease (*Kennedy et al 1985*). Other reports demonstrated that frequent PVCs in apparently healthy individuals are associated with increased risk of all cause mortality and sudden cardiac death (*Bikkina et al 1992*). However, these studies lacked rigorous measures to exclude underlying heart disease. Several studies demonstrated that PVCs more than 10-20 thousands/24 hours or more than 10-20% of total beats/24 hours can lead to cardiomyopathy which is usually reversible after medical or ablative therapy (*Efremidis M et al 2008*).

The majority of idiopathic PVCs originate from the right ventricular outflow tract (RVOT) (*Kiatchoosakul et al 1999*). Symptoms range from minor discomfort (or no symptoms) to incapacitating palpitations, presyncope and syncope (*Kennedy et al 1976*). Symptomatic patients benefit from

pharmacotherapy or ablation. The mainstay of pharmacotherapy is β -blockers and non-dihydropyridine calcium antagonists. However, patients with contraindications or no response to these medications are challenging to treat. The safety profile of class Ia, Ic, and III antiarrhythmic drugs is considered a limitation for the long term treatment of an arrhythmia of benign nature

Mexiletine; a class Ib antiarrhythmic drug, was shown to be effective in treating ventricular arrhythmias with no reported proarrhythmias related to repolarization changes. The antiarrhythmic effect of mexiletine has been established in controlled comparative trials against placebo, quinidine, procainamide and disopyramide. Mexiletine at doses of 600 to 1200 mg/day produced a significant reduction of PVCs, paired beats, and episodes of non-sustained ventricular tachycardia (NSVT) compared to placebo, and was similar in effectiveness to other class I agents (Mason et al 1993). Follow-up of patients from the controlled trials has demonstrated continued effectiveness of mexiletine in long-term use (Talbot et al 1976)

The main adverse effects of mexiletine are related to upper gastrointestinal and central nervous system (Monk et al 1990). Mexiletine does not cause significant hemodynamic effects, conduction defects, or QT interval prolongation (Talbot et al 1976).

(Chapter 1: prevalence and evaluation of PVCs

Up to our knowledge, no comparative studies demonstrated the efficacy and safety of mexiletine versus a atenolol in apparently healthy subjects for the treatment of idiopathic PVCs.

Prevalence and evaluation of premature ventricular contractions

INTRODUCTION:

Ventricular premature beats (VPBs), also called ventricular extrasystoles (VEs) or premature ventricular contractions (PVCs) or depolarizations, are common and occur in a broad spectrum of the population, including those with and without structural heart disease, irrespective of its severity (Satish et al, 2005).

PVCs are commonly diagnosed during examination or routine electrocardiographic (ECG) recording. In these settings, they are best ignored because symptoms are usually trivial and there is no evidence that suppression (even in patients with heart disease) can extend life expectancy or reduce the risk of an untoward arrhythmic event.

Some of the issues relating to PVCs, including epidemiology, classification, etiology, and evaluation, will be reviewed here. The clinical significance and the treatment of PVCs are discussed separately.

PREVALENCE AND DISEASE ASSOCIATIONS:

The prevalence of PVCs is directly related to the study population, the detection method, and the duration of observation. The following findings were noted in a review of 15,792 middle-aged subjects in the Atherosclerosis Risk in Communities (ARIC) study (Simpson et al, 2002):

- The overall prevalence of any PVC on a two minute ECG was approximately 6 percent; the prevalence of more frequent or complex PVCS (multiformed, couplets, or nonsustained ventricular tachycardia) was approximately 3 and 0.8 percent, respectively.
- PVCs were more frequent in men than women, in African-Americans compared to whites, and in those with organic heart disease.
- The prevalence of PVCs increased with age (34 percent increase for each five year increment in age) and in the presence of other factors, such as faster sinus rate, hypokalemia, hypomagnesaemia, and hypertension.

However, prevalence estimates in epidemiologic studies are of uncertain accuracy, because the ability to detect PVCS is dependent upon the duration of observation. The longer an individual is monitored (eg, 24 hours of ambulatory monitoring), the more likely a PVC will be detected.

In epidemiologic studies, a two minute rhythm strip is often used to detect PVCs. The utility of this approach was assessed in a series of 242 patients referred for ambulatory ECG monitoring (*Evenson et al, 2000*). The presence of PVCs is an insensitive predictor of PVCs on 24 hour monitoring. Thus, a two minute ECG rhythm strip is not a useful clinical screening tool to detect PVCs (*Evenson et al, 2000*).

Normal individuals:

When a resting 12-lead ECG is used, PVCs are infrequent in patients with no known heart disease *(Chiang et al, 1969)*. By comparison, when 24-hour ambulatory monitoring is used, up to 80 percent of healthy men or women have PVCs *(Sobotka et al, 1981)*.

As indicated above, there is an age related increase in the prevalence of PVCs in normal individuals and those with underlying heart disease (Simpson et al, 2002).

Mitral valve prolapse:

All forms of ventricular as well as supraventricular arrhythmia are common in patients with mitral valve prolapse (*Schaal et al, 1992*). PVCs are seen in 58 to 89 percent of these patients and complex ventricular arrhythmia (multiformed PVCs, couplets or nonsustained ventricular tachycardia) occurs in 30 to 56 percent (*Schaal et al, 1992*).

The mechanisms of ventricular ectopy include:

- Abnormal tension or stretch on the papillary muscles or chordae tendineae.
- Mechanical irritation of the endocardium by thickened chordae tendineae.
- Contraction abnormalities due to a localized cardiomyopathy.
- Alterations in autonomic tone.
- Abnormalities of repolarization.

Although frequent PVCs have been reported in up to 89 percent of adults with mitral valve prolapse, it is unclear if any arrhythmia, including PVCs, is more common in patients with mitral valve prolapse than in normals. However, patients with mitral valve prolapse who have redundant mitral leaflets and mitral regurgitation may have an increased frequency and complexity of PVCs (Kligfield et al, 1985). In this setting, the frequency of PVCs is related to the hemodynamic abnormality rather than the prolapse itself (Kligfield et al, 1985).