

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

عَلَيْكَ عَظِيمًا

صَلَّى اللَّهُ عَلَيْكَ

The Potential Role of Ivabradine Versus Metoprolol in Experimental Models of Atherosclerosis, Myocardial Infarction and Dysrhythmia in Rats

Thesis

Submitted for Partial Fulfillment of M.D in
Pharmacology & Therapeutics

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2012

Acknowledgement

First of all, I would like to thank Allah.

I would like to express my deepest gratitude and great respect to Prof. Dr. Hoda Abdel Gelil Sallam, Professor of Pharmacology and Therapeutics, Faculty of Medicine, Ain Shams University, I had the honor and pleasure to proceed with work under her supervision. Her constant guidance and encouragement made all the difference.

I'd like to express my deepest thanks to Prof. Dr. Ahmed El Sayed Badawy, Professor of Pharmacology and Therapeutics, Faculty of Medicine, Ain Shams University, for his continuous guidance, encouragement, creativity and offering me his precious time for clinical experience.

My deepest appreciation goes to Dr. Hala Salah Abdel Kawy, Assistant Professor of Pharmacology and Therapeutics, Faculty of Medicine, Ain Shams University, for her valuable suggestions, advice, effort and for allowing me a free access to her precious time during the accomplishment of this work.

Special thanks goes to Dr. Ghada Farouk Mohamed, Assistant Professor of Histology, Faculty of Medicine, Ain Shams University, for her help and co-operation without which this work could not be possible.

And last but not least, I would like to thank Dr. Amany Helmy Mohamed, Lecturer of Pharmacology and Therapeutics, Faculty of Medicine, Ain Shams University for her patience, support and valuable supervision which made this work possible.

Nervien Hendawy

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List of Abbreviations

b-AR	β -adrenergic receptor
AC	Adenylyl cyclase
ACE	Angiotensin converting enzyme
Ach	Acetylcholine
ApoE	Apolipoprotein E
AT1	Angiotensin receptor 1
AV	Atrioventricular
bpm	Beats per minute
CAD	Coronary artery disease
cAMP	Cyclic adenosine monophosphate
CCBs	Calcium channel blockers
cGMP	Cyclic guanosine monophosphate
CK	Creatine kinase
CK-MB	Creatine kinase MB isoenzyme
CNBD	Cyclic nucleotide-binding domain
COX-2	Cyclooxygenase 2
CVD	Cardiovascular disease
CYP	Cytochrome P
DNA	Deoxyribonucleic acid
EC₅₀	Effective concentration 50
ECG	Electrocardiographic
ELISA	Enzyme-linked immunosorbent assay
E_{max}	Maximum contractile response
eNOS	Endothelial Nitric Oxide Synthase
ET1	Endothelin 1
G_{αi}	G-protein α subunit inhibitory
G_{αs}	G-protein α subunit stimulatory
G_{βγ}	G-protein $\beta\gamma$ subunit
GFR	Glomerular filtration rate
H&E	Hematoxylin-Eosin stain
v	
HCN	Hyperpolarization activated cyclic nucleotide-gated

HR	Heart rate
HRR	Heart rate reduction
I/M	Intima/media
LDH	Lactic dehydrogenase
LDL	Low density lipoprotein
L-NAME	<i>N</i> -nitro-L-arginine methyl ester
LV	Left ventricular
LV dP/dt	Derivative of left ventricular pressure over time
M2	Type-2 muscarinic receptor
MCP-1	Monocyte chemotactic protein-1
MI	Myocardial infarction
mRNA	Messenger ribonucleic acid
NAD	Nicotinamide adenine dinucleotide
NADH	1, 4 dihydronicotinamide adenine dinucleotide
NADPH	Nicotinamide adenine dinucleotide phosphate
NIH	National Institute of Health
NO	Nitric oxide
PI3	Phosphatidylinositol 3
PVC	Premature ventricular contraction
SAN	Sinoatrial node
SBP	Systolic blood pressure
SEM	Standard error of mean
SS	Shear stress
TMB	Tetramethyl benzidine substrate
TS	Tensile stress
TSP-4	Thrombospondin-4 gene
UV	Ultraviolet
VF	Ventricular fibrillation
VFT	Ventricular fibrillation threshold
V_{max}	Maximum rate of depolarization
VT	Ventricular tachycardia

Aim: This study was designed to investigate the effects of ivabradine versus metoprolol on cardiovascular changes and the infarction size induced by isoprenaline in chronic *N*-nitro-L-arginine methyl ester (L-NAME) treated rats and digoxin induced ventricular dysrhythmia.

Methods: Experiment one, four groups of male Wistar rats were studied: control group, L-NAME treated group (100mg/kg), L-NAME (100mg/kg) and ivabradine (10mg/kg) treated group and L-NAME (100mg/kg) and metoprolol (150mg/kg) treated group. All treatments were administered daily by gavage. After 6 weeks of L-NAME treatment myocardial infarction was induced by isoprenaline injection (11mg/100g/day i.p. for 2 consecutive days). Experiment two, three groups of rats were studied: digoxin, ivabradine and metoprolol groups. Systolic blood pressure and electrocardiograph were monitored. Cardiac marker enzymes were measured and histopathological examination of heart tissues, aorta and coronary vessels were performed. Vascular reactivity of the isolated aortic ring was done. **Results:** Ivabradine and metoprolol administration to L-NAME/ isoprenaline treated rats significantly reduced heart rate, microvascular remodeling, the infarct size, serum lactate dehydrogenase and creatine kinase and attenuated the mortality resulting from isoprenaline induced infarction. Treatment with ivabradine had non-significant effect against L-NAME induced hypertension and cardiac hypertrophy, while metoprolol had a significant effect. Ivabradine improves endothelial function, and reduces atherosclerotic plaque formation in L-NAME treated rats. On the contrary, metoprolol reduced atherosclerosis in L-NAME treated rats with no effect on endothelial function. Ivabradine could not protect against digoxin induced ventricular dysrhythmia while metoprolol showed protective effect. **Conclusion:** These results suggest that ivabradine has a significant protective effect against isoprenaline-induced myocardial infarction, endothelial dysfunction and atherosclerosis in chronic L-NAME-treated rat.

Key words: Ivabradine; metoprolol; *N*G-nitro-L-arginine methyl ester (L-NAME); atherosclerosis.

الهدف: صمم هذه البحث لدراسة آثار الأيفابرادين مقارنةً بالميثوبرولول على التغيرات في القلب والأوعية الدموية وحجم احتشاء الناجم عن حقن مادة الأيزوبرينالين في نموذج حيواني يتم فيه منع مزمن لصناعة أوكسيد النيتريك عن طريق معالجة الفئران بمادة (L-NAME) والإيثانول. ضربات القلب المحدثة بمادة الديجوكسين. طرق البحث: قسمت - - - إلى أربع مجموعات: مجموعة السيطرة ومجموعة معالجة بمادة L-NAME /مجم/ كجم ومجموعة معالجة بمادة L-NAME /مجم/ كجم والأيفابرادين /مجم/ كجم ومجموعة معالجة بمادة L-NAME /مجم/ كجم والميثوبرولول /مجم/ كجم. و قد تم إعطاء هذه الأدوية يومياً عن طريق أنبوب معدي لمدة ١٤ أسابيع. بعد ستة أسابيع من العلاج بمادة L-NAME تم إحداث احتشاء عضلة القلب عن طريق الحقن البيرتوني لمادة الأيزوبرينالين بجرعة ١٠٠ مجم لكل ١٠٠٠ جرام من وزن الجسم لمدة يومين متتاليين. و بعد ذلك تم قياس ضغط الدم المباشري ورسم القلب. و قياس انزيمات القلب في الدم ودراسة التغيرات المرضية في أنسجة القلب و الشرايين التاجية والشريان الأورطي. دراسة تغيرات وظائف الخلايا المبطنة لحلقات الشريان الأبهر المعزولة. وفي الثانية تم دراسة ثلاث مجموعات من الفئران: مجموعة معالجة الديجوكسين وأخرى بالأيفابرادين وأخرى بالميثوبرولول. **النتائج:** إعطاء الأيفابرادين و الميثوبرولول للفئران المعالجة بمادة L-NAME/isoprenaline قد أحدث انخفاض ملحوظاً في معدل ضربات القلب والتغيرات المرضية في الأوعية الدموية الدقيقة حجم احتشاء القلب ومستوى الكرياتينين كيناز - (م ب) واللاكتيك ديهيدروجيناز في الدم ومعدل الوفيات الناجم عن الأيزوبرينالين. إعطاء الأيفابرادين لم يكن له تغيير ذي دلالة إحصائية في ضغط الدم الانقباضي أو قطر القلب على عكس الميثوبرولول الذي أحدث تغييراً ذا دلالة إحصائية. وأحدث الأيفابرادين تحسناً في وظيفة الأوعية الدموية وتصلب الشرايين في الفئران المعالجة بمادة L-NAME. على العكس من ذلك الميثوبرولول من تصلب الشرايين بدون أي تأثير على وظيفة بطانة الأوعية الدموية. لم يستطع الأيفابرادين الوقاية ضد اختلال ضربات القلب البطيني الناجم عن الديجوكسين تحت ظروف التجربة المستخدم. حين أظهر الميثوبرولول تأثير وقائي. **النتيجة:** تشير هذه النتائج إلى أن الأيفابرادين له تأثير وقائي ضد احتشاء عضلة القلب الناجم عن مادة الأيزوبرينالين وظيفية الأوعية الدموية وتصلب الشرايين في الفئران الخاضعة للعلاج المزمن بمادة L-NAME.

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2009

الدور المحتمل للايفابرادين بالمقارنة مع الميتوبرولول في نماذج تجريبية
لتصلب الشرايين، الذبحة الصدرية واختلال ضربات القلبية
في الفئران

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