بسم الله الرحمن الرحيم

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تم رفع هذه الرسالة بواسطة / سامية زكى يوسف

بقسم التوثيق الإلكتروني بمركز الشبكات وتكنولوجيا المعلومات دون أدنى مسئولية عن محتوى هذه الرسالة.

ملاحظات: لا يوجد

Effects of Ivabradine on Neopterin and NT-Pro BNP in Patients with Congestive Heart Failure

Thesis

Submitted for Master's degree (M.Sc.) in Pharmaceutical Science (Clinical Pharmacy)

By

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2022

Acknowledgment

First of all, I would like to express my intense gratitude to **ALLAH** for guiding my steps and his countless blessings. The completion of my thesis took me a long journey of trial and error, patience and persistence. I would like to take this as an opportunity to thank my committee of supervisors who helped and guided me throughout the whole journey. I am very grateful for their supervision and I owe them my greatest appreciation.

I would like to show my gratitude to **Prof. Dr. Gamal Omran**, Professor of Biochemistry and Dean of Faculty of Pharmacy, Damanhour University. An inquisitive, supportive and experienced role model whose vision has enlightened me throughout the way. It is my honour to continue this work under your supervision.

I would also like to express how lucky I am to be under the supervision of **Prof. Dr. Sahar El-Haggar,** Professor of Clinical Pharmacy, Tanta University. A well experienced model in the field of clinical pharmacy whose continuing guidance have led to success of my research. Her valuable comments were critical in improving this thesis greatly.

I would like to express how fortunate I am to have **Dr. Rehab Werida,** Associate Professor of Clinical Pharmacy, Damanhour University as my supervisor. A hardworking, helpful and supportive person. Thank you for giving me the time and attention during the whole period of my master's degree.

I am greatly thankful to **Dr. Ibtesam Khairat Abdelhai**, Associate Professor of Cardiology of Faculty of Medicine, Tanta University. For her to dedicate so much time to help and facilitate the success of this research. Moreover, for providing important tips throughout the whole process.

I would love to express my gratitude and sentiments to my **family**. To my Mother, always being there for me, supporting me in every step, and trying to figure out the way for each obstacle that faces me during my research. To my Father, Professor of Anaesthesiology, Faculty of Medicine, Alexandria University, who was with me in every step, helping me with every part of my research, being supportive and offering valuable tips. To my brother who tried his best to cheer my up when things weren't working out and for reminding me how good and successful I am that I can achieve almost anything. I am well aware that I will forever be indebted to all of you and no matter what I do, I won't be able to pay you back for everything that you have done to me.

List of Abbreviations

ACEIs: Angiotensin Converting Enzyme Inhibitors

ADH: Anti-Diuretic Hormone

AF: Atrial Fibrillation

AHA: American Heart Association

ALT: Alanine Transaminase

ANP: Atrial Natriuretic Peptide

ARB: Angiotensin Receptor Blocker

ARBs: Angiotensin Receptor Blockers

ARNI: Angiotensin receptor blocker/Neprilysin Inhibitors

AST: Aspartate Transaminase

BNP: Brain Natriuretic Peptide

BUN: Blood Urea Nitrogen

CHF: Congestive Heart Failure

CKD: Chronic Kidney Disease

CNP: C-type Natriuretic Peptide

CNS: Central Nervous System

CO: Cardiac Output

COPD: Chronic Obstructive Pulmonary Disease

CRP: C-Reactive Protein

EF: Ejection Fraction

ECG: Electro-Cardiogram

ESC: European Society of Cardiology

HF: Heart Failure

HFpEF: Heart Failure preserved Ejection Fraction

List of Abbreviations

HFrEF: Heart Failure reduced Ejection Fraction

H-ISDN: Hydralazine Isosorbide Dinitrate

HR: Heart Rate

I_f: Funny Current

$I_{h:}$ hyperpolarization-activated current

IHD: Ischemic Heart Disease

LVEDP: Left Ventricular End Diastolic Pressure

LVEDV: : Left Ventricular End Diastolic Volume

MAP: Mean Arterial Pressure

MRA: Mineralocorticosteroid Antagonist

NP: Natriuretic Peptide

NSAIDs: Non-steroidal Anti-inflammatory

NT-Pro BNP: N-Terminal pro Brain Natriuretic Peptide

NYHA: New York Heart Association

OD: Optical Density

RAAS: Renin Angiotensin Aldosterone System

SAN: Sino Atrial Node

Scr: Serum Creatinine

SGLT-2: Sodium-Glucose Co-transporter 2

SNS: Sympathetic Nervous System

TPR: Total Peripheral Resistance

Declarations

I declare that no part of this work had been submitted for another degree or qualification in any university or other institution of learning.

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Signature:

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Abstract

Background: Heart rate (HR) reduction is a cornerstone in heart failure (HF) therapy to improve patient outcomes. The aim of this study is to evaluate short term effect of ivabradine on NT-Pro BNP and neopterin in heart failure patients and assess the association between HR and these biomarkers.

Methods: A double blinded, parallel interventional study including sixty patients randomly allocated into ivabradine (5 mg twice daily) or non-ivabradine group (n=30, each) for 3 months. Lipid profile and kidney functions were performed and blood samples for NT-Pro BNP and neopterin were analysed at baseline and after 3 months of intervention in both groups.

Results: There was a significant improvement in NYHA class in ivabradine group ($p < 0.001$). Ejection fraction was improved in both groups after intervention ($p < 0.001$), with a greater improvement in ivabradine group ($p=0.026$). Heart rate was reduced in both groups ($p < 0.001$) with greater reduction in ivabradine group ($p < 0.001$). NT-Pro BNP and neopterin levels significantly decreased in ivabradine group ($p < 0.001$). Significant positive correlation was found between HR and biomarkers levels after intervention (NT-Pro BNP: $p < 0.001$, neopterin: $p=0.002$)**.**

Conclusion: Ivabradine therapy reduced levels of both biomarkers which correlated well with HR. Biomarkers levels might provide a tool for assessing ivabradine effectiveness in HF.

1. Introduction

Congestive heart failure (CHF) is a complex clinical syndrome that can result from any functional or structural cardiac disorder that impairs the ventricles ability to fill with or eject blood [1–4]. According to European Society of Cardiology (ESC) guidelines, pharmacological therapy for HF includes the use of angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blocker/neprilysin inhibitor (ARNI) in addition to beta-blockers, mineralocorticoid antagonist (MRA) and dapagliflozin/empagliflozin as first line therapy to reduce hospitalization and mortality. In case of intolerance to ACEIs or ARNI, angiotensin receptor blockers (ARBs) are the alternative choice. Loop diuretics are used only to improve signs and symptoms of congestion with no effect on morbidity or mortality. Other agents include, digoxin, hydralazine-isosorbide dinitrate (H-ISDN), and ivabradine [5,6].

Ivabradine is an I_f current inhibitor. The selective and specific inhibition of the cardiac pacemaker I_f current controls the spontaneous diastolic depolarization in the sinus node and regulates HR. Ivabradine is indicated in CHF NYHA II -- IV class with systolic dysfunction, in patients in sinus rhythm and whose HR is ≥70 bpm, in combination with standard therapy including Beta-Blocker therapy or when Beta-blocker therapy is contraindicated or not tolerated [7,8].

To assess the efficacy of ivabradine therapy, HR was measured at definite intervals. Cardiac biomarkers have been related to the morbidity and mortality in HF patients. Example of those biomarkers are N-terminal-pro hormone BNP (NT-Pro BNP) and neopterin. It has been demonstrated that both levels of NT-Pro BNP and neopterin are elevated in patients with HF NYHA class 2-4 [9–16]. Moreover, traditional therapies of HF demonstrated their ability to decrease

those biomarkers as a part of their role to improve the patient's condition. Thus, the use of both biomarkers is promising to assess efficacy of drugs used in the management of CHF [9,12–14,16,17]. The aim of this study is to assess the efficacy of ivabradine therapy in patients with CHF using the cardiac biomarkers NT-Pro BNP and neopterin. . Also, to assess the correlation between those biomarkers in CHF patients.

2. Review of literature

2.1 Definition and classification:

Congestive heart failure (CHF) is a complicated clinical condition that affects the ability of the heart ventricles to fill up or pump enough blood to meet requirements of the body [2,3]. The incidence of HF increases with age reaching a peak in those older than 65 years [2,3]. CHF can be classified based on mechanism of dysfunction into either systolic or diastolic HF [3]. In systolic HF, the ventricles are unable to contract fully to pump enough blood to meet body requirements of oxygen and nutrients and thus, ejection fraction (EF) is reduced i.e. heart failure with reduced ejection fraction (HFrEF) [3]. While in diastolic HF, ventricles can't fill adequately probably due to stiffening or hypertrophy that prevent their expansion, yet they have enough power to pump the blood to the rest of the body thus, EF is preserved i.e. Heart failure with preserved ejection fraction (HFpEF) [3].

There are a variety of causes of HF, hypertension, ischemic heart disease (IHD) and diabetes seem to be the most common ones among patients with HF[1–3,18]. Other causes of HF might include: cardiomyopathies, valvular heart disease, atrial fibrillation (AF), chronic kidney disease (CKD), obstructive pulmonary disease (COPD), thyroid dysfunction and anaemia [1–3,18].

2.2 Pathophysiology of heart failure:

The mechanism underlying the development of HF is not fully understood. A number of variables are responsible for the final consequences seen in HF patients [2,3]. Cardiac output (CO) which is the volume of blood pumped per minute is determined by both stroke volume and HR, Stroke volume being volume of blood pumped per beat while HR is the number of beats per minute [3,19]. Stroke volume is further determined by 3 variables: preload, afterload and contractility. Preload is the resistance the heart must pump against while afterload is the volume of blood returning to the