

A Pharmacokinetic Study of Ivabradine and Bisoprolol Combination in Healthy Volunteers

A thesis submitted for the fulfillment of Master Degree in Pharmaceutical science
(Clinical Pharmacy)

Submitted By

Raghda Saady Alsharkawy, B.Sc

Clinical Pharmacist

Misr International University

2007

Under supervision of

Prof. Dr. Nagwa Ali Sabri

Professor and Head of Clinical Pharmacy Department

Faculty of Pharmacy

Ain shams university

Dr. Sara Mahmoud Zaki

Lecturer of Clinical Pharmacy

Faculty of Pharmacy

Ain shams university

2019

Acknowledgment

I am deeply thankful to "Allah" by the grace of whom, this work was possible.

I would like to express my deep appreciation and gratitude to prof. Dr. Nagwa Ali Sabri, head of clinical pharmacy department - faculty of pharmacy - Ain Shams University, for her sincere help, valuable guidance and continuous support in completing this work.

I'm greatly indebted to Dr. Sara Mahmoud Laki, lecture of clinical pharmacy - faculty of pharmacy - Ain Shams University, for her kind help, guidance and follow up throughout the whole work. She spared no efforts or time through this research.

I would like to thank all members of clinical pharmacy department, faculty of pharmacy - Ain shams university, for their continuous support.

Many special thanks and deep gratitude to my beloved parents and my elder sister who always encourage and support me.

I express deep and sincere gratitude to my dear sisters and brothers for their continuous love and care.

I would like to thank all my family and friends for their kind and sincere help, love and support during the progress of this work and sure I will not forget to thank Drug Research Center and all staff there and special thanks for all helpful volunteers.

Finally, I would like to thank the most important and most precious person in my life, who lived with me all events and he was a very nice supporter for me, without him I can't reach for this stage. Unfortunately he is gone from life now but I have faith in God that he now feels me.

List of Contents

	Page
List of abbreviations	IV
List of tables	VI
List of figures	IX
Abstract	XIV

Literature Review

I. Heart Failure

• Definition	1
• Etiology	1
• Pathophysiology	1
• Risk factors	3
• Epidemiology	4
• Classification	5
• Stages according to American Heart Association	6
• Treatment: -Non Pharmacological treatment . -Pharmacological treatment.	7
A)-Diuretic	7
B)-Neurohormonal blocking agent	11
C)-Digoxin	17
D)-N-3 polyunsaturated fatty acids	18
E)-Other Drugs	19
F)-Calcium channel blockers	20
G)-Ivabradine	23

II. Ivabradine	
Mechanism of action	24
Pharmacokinetics	24
Dosage Form	25
Dosing	25
Dose adjustment in special population	25
Labeled Indication	27
Adverse drug Reaction	28
Contraindication	28
Drug interactions	28
Monitoring Parameters	29
 III. Bisoprolol	
Mechanism of action	30
Pharmacokinetics	30
Dosage Form	31
Dosing	31
Dose adjustment in special population	32
Labeled Indication	32
Adverse drug Reaction	33
Contraindication	33
Drug interactions	34
Monitoring Parameters	35
 IV. Clinical pharmacokinetic: the role of clinical pharmacist	36

Aim of the work	
Aim of the work	39
Subjects and Methods	
I. Method development and validation	40
II. <i>In vivo</i> study	52
Results	
I. Bioanalytical method validation	64
II. <i>In vivo</i> study	74
III.Safety	117
Discussion	
Discussion	119
Limitation and Recommendation	121
Summary	122
References	125
Arabic summary	

List of abbreviations

ACC/AHA/HFSA	American College of Cardiology/American Heart Association /Heart Failure Society of America
ACCP	American College of Clinical Pharmacy
ACEI	Angiotensin converting enzyme inhibitor
AHF	Acute Heart Failure
ARBs	Angiotensin receptor blockers
ARNI	Angiotensin receptor neprilysin inhibitor
AT2 antagonist	Angiotensin receptor subtype 2
AUC_{0-∞}	Area under plasma concentration –time curve from zero to infinity
AUC_{0-t}	Area under plasma concentration –time curve from zero to time t
β Blocker	Beta blocker
BMI	Body mass index
CAD	Coronary artery disease
cGMP	Cyclic guanosine monophosphate
CHD	Congestive heart disease
CHF	Congestive heart failure
CI	Confidence Interval
%CV	Percent Coefficient of Variation
CYP3A4	Cytochrome P3A4
DHA	Docosaheptaenoic acid
ECG	Electro cardio gram
FDA	Food and drug Administration
GMR	Geometric Mean Ratio
HF	Heart Failure
HF_{rEF}	Heart Failure with reduced ejection fraction
HPLC	High performance liquid chromatography
ICH	International conference of harmonization
Ke	Rate of elimination
LVEF	Left ventricular ejection fraction
MI	Myocardial infarction
MRA	Mineralocorticoid receptor antagonist
MRT	Mean residence time
NT-ProBNP	B-type natriuretic peptide and N-type natriuretic peptide
NYHA	New York Heart Association

PK/PD	Pharmacokinetic-Pharmacodynamic
PUFAs	Poly unsaturated fatty acids
QC	Quality control
QOL	Quality of life
RAAS	Renin angiotensin aldosterone system
SA node	Sinoatrial node
SD	Standard deviation
T_{1/2}	Elimination half life
T_{max}	Time to reach maximum plasma concentration
Vd	Volume of distribution

List of Tables

Number	Title	Page
Table (i)	Classification of Heart Failure	5
Table(ii)	Master standard solution(Ivabradine)	42
Table(iii)	Master standard solution (Bisoprolol)	43
Table(iv)	Preparation of Calibration Standards (Ivabradine)	45
Table(v)	Preparation of Calibration Standards (Bisoprolol)	45
Table(vi)	Chromatographic Conditions	46
Table(vii)	General MS parameters	47
Table(viii)	Ion Source Parameters	47
Table(ix)	Preparation of Quality Control Samples (Ivabradine)	48
Table(x)	Preparation of Quality Control Samples (Bisoprolol)	48
Table(xi)	Randomization Schedule	56
Table(1)	Intra-day Accuracy Data (Ivabradine).	68
Table(2)	Intra-day precision Data (Ivabradine).	69
Table(3)	Analytical Precision for the Analysis of Ivabradine performed on three sets of Standard Curves on the same day	69
Table(4)	Accuracy determination of Ivabradine in Plasma	70
Table(5)	Intra-day Accuracy Data (Bisoprolol).	71
Table(6)	Intra-day precision Data (Bisoprolol)	71
Table(7)	Analytical Precision for the Analysis of Bisoprolol performed on three sets of Standard Curves on the same day	72
Table(8)	Accuracy determination of Bisoprolol in Plasma	72
Table(9)	Quality Control Samples Definition for Ivabradine	73
Table(10)	Quality Control Samples Definition for bisoprolol	73

Table(11)	Demographic characteristics for volunteers who participated in the study.	76
Table(12)	Vital Sign Data of Volunteers participated in period I in the study	77
Table(13)	Vital Signs of Volunteers Participated in period II in the study	78
Table(14)	Vital Signs of Volunteers participated in period III in the study.	79
Table(15)	Biochemical Data of Volunteers participated in the study	80
Table(16)	Complete Blood Picture Report.	81
Table(17)	Urine Analysis Report	82
Table(18)	Ratio analysis of Untransformed and Ln-transformed C_{max} (ng/ml) data of Ivabradine after single dose administration of Ivabradine alone and Ivabradine/Bisoprolol combination.	109
Table(19)	Ratio analysis of Untransformed and Ln-transformed AUC_{0-t} data of Ivabradine after single dose administration of Ivabradine alone and Ivabradine/Bisoprolol combination.	110
Table(20)	Ratio analysis of Untransformed and Ln-transformed AUC_{0-inf} data of Ivabradine after single dose administration of Ivabradine alone and Ivabradine/Bisoprolol combination.	111

Table(21)	Ratio analysis of Untransformed and Ln-transformed $C_{\max}$ (ng/ml) data of Bisoprolol after single dose administration of Bisoprolol alone and Bisoprolol /Ivabradine combination.	112
Table(22)	Ratio analysis of Untransformed and Ln-transformed AUC_{0-t} data of Bisoprolol after single dose administration of Bisoprolol alone and Bisoprolol /Ivabradine combination.	113
Table(23)	Ratio analysis of Untransformed and Ln-transformed AUC_{0-inf} data of Bisoprolol after single dose administration of Bisoprolol alone and Bisoprolol /Ivabradine combination.	114
Table(24)	Pharmacokinetic parameters of ivabradine after single oral administration of 10 mg alone	115
Table(25)	Pharmacokinetic parameters of bisoprolol after single oral administration of 5 mg alone or co-administered with ivabradine 10 mg	116
Table(26)	Adverse Event(s) & Side Effect(s) Recorded in Participants during the three Periods of Ivabradine 10mg / Bisoprolol 5mg Film Coated Tablet Pharmacokinetics Interaction Study	118

List of Figures

Figure No.	Title	Page
Figure(I)	Pathophysiological mechanisms of heart failure & major sites of drug action.	3
Figure(II)	Molecular structure of ivabradine	24
Figure(III)	Molecular structure of bisoprolol	30
Figure(IV)	Study design	54
Figure(1)	Sample chromatograms	64
Figure(2)	Representative chromatograms for blank plasma sample.	65
Figure(3)	Representative chromatograms for blank plasma sample and plasma samples from volunteer after 12 hours of administration of Ivabradine	66
Figure(4)	Mean Calibration plot of Ivabradine in human plasma	67
Figure(5)	Mean Calibration plot of Bisoprolol in human plasma	67
Figure(6)	Linear(above) and semi-logarithmic plot for <u>Volunteer No.1</u> Bisoprolol plasma concentration (ng/ml) after single dose administration of Treatment A ₁ Concor [®] 5mg Film Coated Tablet and Treatment B Ivabradine 10mg and Bisoprolol 5mg.	83
Figure(7)	Linear(above) and semi-logarithmic plot for <u>Volunteer No.2</u> Bisoprolol plasma concentration (ng/ml) after single dose administration of Treatment A ₁ Concor [®] 5mg Film Coated Table and Treatment B Ivabradine 10mg and Bisoprolol 5mg	84

Figure(8)	Linear(above) and semi-logarithmic plot for <u>Volunteer No.3</u> Bisoprolol plasma concentration (ng/ml) after single dose administration of Treatment A ₁ Concor [®] 5mg Film Coated Tablet and Treatment B Ivabradine 10mg and Bisoprolol 5mg.	85
Figure(9)	Linear (above) and semi-logarithmic plot (below) for <u>Volunteer No.4</u> Bisoprolol plasma concentration (ng/ml) after single dose administration of Treatment A ₁ Concor [®] 5mg Film Coated Tablet and Treatment B Ivabradine 10mg and Bisoprolol 5mg.	86
Figure(10)	Linear (above) and semi-logarithmic plot (below) for <u>Volunteer No.5</u> Bisoprolol plasma concentration (ng/ml) after single dose administration of Treatment A ₁ Concor [®] 5mg Film Coated Tablet and Treatment B Ivabradine 10mg and Bisoprolol 5mg.	87
Figure(11)	Linear (above) and semi-logarithmic plot (below) for <u>Volunteer No.6</u> Bisoprolol plasma concentration (ng/ml) after single dose administration of Treatment A ₁ Concor [®] 5mg Film Coated Tablet and Treatment B Ivabradine 10mg and Bisoprolol 5mg.	88
Figure(12)	Linear (above) and semi-logarithmic plot (below) for <u>Volunteer No.7</u> Bisoprolol plasma concentration (ng/ml) after single dose administration of Treatment A ₁ Concor [®] 5mg Film Coated Tablet and Treatment B Ivabradine 10mg and Bisoprolol 5mg.	89

Figure(13)	Linear (above) and semi-logarithmic plot (below) for <u>Volunteer No.8</u> Bisoprolol plasma concentration (ng/ml) after single dose administration of Treatment A ₁ Concor [®] 5mg Film Coated Tablet and Treatment B Ivabradine 10mg and Bisoprolol 5mg.	90
Figure(14)	Linear (above) and semi-logarithmic plot (below) for <u>Volunteer No.9</u> Bisoprolol plasma concentration (ng/ml) after single dose administration of Treatment A ₁ Concor [®] 5mg Film Coated Tablet and Treatment B Ivabradine 10mg and Bisoprolol 5mg.	91
Figure(15)	Linear (above) and semi-logarithmic plot (below) for <u>Volunteer No.10</u> Bisoprolol plasma concentration (ng/ml) after single dose administration of Treatment A ₁ Concor [®] 5mg Film Coated Tablet and Treatment B Ivabradine 10mg and Bisoprolol 5mg.	92
Figure(16)	Linear (above) and semi-logarithmic plot (below) for <u>Volunteer No.11</u> Bisoprolol plasma concentration (ng/ml) after single dose administration of Treatment A ₁ Concor [®] 5mg Film Coated Tablet and Treatment B Ivabradine 10mg and Bisoprolol 5mg.	93
Figure(17)	Linear (above) and semi-logarithmic plot (below) for <u>Volunteer No.12</u> Bisoprolol plasma concentration (ng/ml) after single dose administration of Treatment A ₁ Concor [®] 5mg Film Coated Tablet and Treatment B Ivabradine 10mg and Bisoprolol 5mg.	94

Figure(18)	Linear (above) and semi-logarithmic plot (below) for <u>Volunteer No.13</u> Bisoprolol plasma concentration (ng/ml) after single dose administration of Treatment A ₁ Concor [®] 5mg Film Coated Tablet and Treatment B Ivabradine 10mg and Bisoprolol 5mg.	95
Figure(19)	Linear (above) and semi-logarithmic plot (below) for <u>Volunteer No.14</u> Bisoprolol plasma concentration (ng/ml) after single dose administration of Treatment A ₁ Concor [®] 5mg Film Coated Tablet and Treatment B Ivabradine 10mg and Bisoprolol 5mg.	96
Figure(20)	Linear (above) and semi-logarithmic plot (below) for <u>Volunteer No.15</u> Bisoprolol plasma concentration (ng/ml) after single dose administration of Treatment A ₁ Concor [®] 5mg Film Coated Tablet and Treatment B Ivabradine 10mg and Bisoprolol 5mg.	97
Figure(21)	Linear (above) and semi-logarithmic plot (below) for <u>Volunteer No.16</u> Bisoprolol plasma concentration (ng/ml) after single dose administration of Treatment A ₁ Concor [®] 5mg Film Coated Tablet and Treatment B Ivabradine 10mg and Bisoprolol 5mg.	98
Figure(22)	Linear (above) and semi-logarithmic plot (below) for <u>Volunteer No.17</u> Bisoprolol plasma concentration (ng/ml) after single dose administration of Treatment A ₁ Concor [®] 5mg Film Coated Tablet and Treatment B Ivabradine 10mg and Bisoprolol 5mg.	99

Figure(23)	Linear (above) and semi-logarithmic plot (below) for <u>Volunteer No.18</u> Bisoprolol plasma concentration (ng/ml) after single dose administration of Treatment A ₁ Concor [®] 5mg Film Coated Tablet [and Treatment B Ivabradine 10mg and Bisoprolol 5mg.	100
Figure(24)	mean plasma concentration of Ivabradine after administration Treatment A2 and Treatment B	101
Figure(25)	mean plasma concentration of Ivabradine after administration Treatment A2 and Treatment B	101
Figure(26)	mean plasma concentration of Bisoprolol after administration Treatment A1 and Treatment B	102
Figure(27)	mean plasma concentration of Bisoprolol after administration Treatment A1 and Treatment B	102
Figure(28)	C _{max} Comparisone between treatment A1 and Treatment B	103
Figure(29)	AUCo-t Comparisoe between Treatment A1 and Treatment B	103
Figure(30)	C _{max} Comparisone between treatment A1 and Treatment B	104
Figure(31)	AUCo-t Comparisoe between Treatment A1 and Treatment B	104