

Prevalence of drug-drug interactions of warfarin prescriptions in South Africa

Stephanie Blaauw

20564430

**Dissertation submitted in partial fulfillment of the requirements for the *degree*
Magister Pharmaciae at the Potchefstroom campus of the North-West
University**

Supervisor: Dr R. Joubert

Co-supervisor: Prof M.S. Lubbe

Co-supervisor: Dr J. Lamprecht

Potchefstroom

October 2012

TABLE OF CONTENTS

CHAPTER 1: INTRODUCTION.....1

1.1	PROBLEM STATEMENT.....	1
1.2	RESEARCH QUESTIONS	3
1.3	RESEARCH OBJECTIVES	4
1.3.1	General research objective	4
1.3.2	Specific research objectives	4
1.3.2.1	<i>Phase 1: Literature review</i>	4
1.3.2.2	<i>Phase 2: Empirical Investigation</i>	5
1.4	RESEARCH METHODOLOGY.....	5
1.4.1	Phase 1: Literature review	5
1.4.1.1	<i>Literature study</i>	5
1.4.2	Phase 2: Empirical investigation	6
1.4.2.1	<i>Research design</i>	6
1.4.2.2	<i>Data source and study population</i>	6
1.4.2.3	<i>Research measurements</i>	6
1.4.2.4	<i>Data analysis</i>	7
1.4.2.5	<i>Ethical considerations</i>	7
1.5	DIVISION OF CHAPTERS.....	7
1.6	CHAPTER SUMMARY	7

CHAPTER 2: OVERVIEW OF WARFARIN AND DRUG-DRUG INTERACTION.....9

2.1	INTRODUCTION.....	9
2.2	THE BACKGROUND OF WARFARIN.....	9
2.2.1	HISTORY	9
2.2.2	PHARMACOLOGICAL CLASSIFICATION	10
2.2.3	INDICATION	10

2.2.4	PHARMACOKINETICS	11
2.2.4.1	<i>Chemistry and stability</i>	11
2.2.4.2	<i>Absorption</i>	12
2.2.4.3	<i>Distribution</i>	13
2.2.4.4	<i>Metabolism</i>	13
2.2.4.5	<i>Warfarin resistance</i>	26
2.2.4.6	<i>Elimination</i>	29
2.2.5	PHARMACODYNAMICS	31
2.2.5.1	<i>Mechanism of action</i>	31
2.2.5.2	<i>Side-effects</i>	34
2.2.5.3	<i>Dosage and monitoring</i>	40
2.2.6	INTERACTIONS	50
2.2.6.1	<i>Introduction</i>	50
2.2.6.2	<i>Mechanisms of drug interactions</i>	53
2.2.6.3	<i>Pharmacokinetic interactions</i>	53
2.2.6.4	<i>Pharmacodynamic interactions</i>	62
2.3	CLINICAL PROBLEM AREAS	63
2.3.1	Adverse drug events	64
2.3.2	Polypharmacy	64
2.3.3	Significance ratings of drug-drug interactions	65
2.4	OTHER ANTICOAGULANTS	72
2.4.1	VITAMIN K ANTAGONISTS	75
2.4.2	HEPARIN AND HEPARIN DERIVATIVES	75
2.4.3	DIRECT THROMBIN INHIBITORS	76
2.4.4	ANTIPLATELET DRUGS	77
2.4.5	FACTOR XA INHIBITORS	79
2.4.6	FIBRINOLYTIC AGENTS	80
2.4.7	ENZYME INHIBITORS	80
2.5	CHAPTER SUMMARY	82
 CHAPTER 3: EMPIRICAL INVESTIGATION.....		83
3.1	AIM	83
3.2	RESEARCH OBJECTIVES	83
3.2.1	GENERAL RESEARCH OBJECTIVE	83
3.2.2	SPECIFIC OBJECTIVES.....	84

3.2.2.1 <i>Empirical Investigation</i>	84
3.3 RESEARCH METHODOLOGY	84
3.3.1 RESEARCH DESIGN	84
3.3.1.1 <i>Pharmacoepidemiology</i>	84
3.3.1.2 <i>Drug utilisation review (DUR)</i>	85
3.3.1.3 <i>The necessity of DUR</i>	85
3.3.1.4 <i>Types of DUR studies</i>	85
3.3.1.5 <i>Cross-sectional studies</i>	87
3.3.2 DATABASE	87
3.3.2.1 <i>Fields</i>	88
3.3.3 STUDY POPULATION	89
3.3.4 CLASSIFICATION SYSTEMS	89
3.3.5 RESEARCH MEASUREMENTS	90
3.3.5.1 <i>Prevalence</i>	90
3.3.5.2 <i>Prescribed daily dose (PDD)</i>	90
3.3.6 DATA ANALYSIS	92
3.3.7 STATISTICAL ANALYSIS	93
3.3.7.1 <i>Average value (mean)</i>	93
3.3.7.2 <i>Standard deviation</i>	94
3.3.7.3 <i>Confidence interval</i>	95
3.3.7.4 <i>Cohens's d-value</i>	96
3.4 RELIABILITY AND VALIDITY OF THE RESEARCH INSTRUMENTS	97
3.5 ETHICAL CONSIDERATIONS	98
3.6 DISCUSSION OF THE RESULTS OF THE EMPIRICAL INVESTIGATION	98
3.7 CONCLUSION AND RECOMMENDATIONS	98
3.8 CHAPTER SUMMARY	98

CHAPTER 4: RESULTS AND DISCUSSION.....99

4.1 CLARIFICATION WITH REGARD TO THE INTERPRETATION OF THE RESULTS	100
4.2 THE GENERAL PRESCRIBING PATTERNS OF MEDICINE ON THE MEDICINE CLAIMS DATABASE	100
4.2.1 GENERAL PRESCRIBING PATTERNS	100
4.2.2 GENERAL PRESCRIBING PATTERNS OF WARFARIN MEDICINE ITEMS	102

4.2.3	NUMBER OF PATIENTS FOR THE SIX YEAR STUDY PERIOD.....	103
4.3	PRESCRIBING PATTERNS OF THE DIFFERENT WARFARIN PRODUCTS	104
4.3.1	DIFFERENT TYPES OF WARFARIN PRODUCTS USED IN SOUTH AFRICA...	104
4.3.2	PRESCRIBING PATTERNS OF WARFARIN PRODUCTS ACCORDING TO DIFFERENT PRESCRIBERS.....	105
4.4	PRESCRIBING PATTERNS OF WARFARIN ACCORDING TO DIFFERENT AGE GROUPS	106
4.4.1	GENERAL PRESCRIBING PATTERNS OF WARFARIN PRESCRIPTIONS ACCORDING TO AGE GROUP	107
4.4.2	NUMBER OF WARFARIN PRESCRIPTIONS PER PATIENT ACCORDING TO AGE	108
4.4.3	FREQUENCY OF WARFARIN MEDICINE ITEMS CLAIMED ACCORDING TO AGE GROUPS	110
4.5	THE PRESCRIBING PATTERNS OF WARFARIN ACCORDING TO GENDER	112
4.5.1	GENERAL PRESCRIBING PATTERNS OF WARFARIN PRESCRIPTIONS ACCORDING TO GENDER	113
4.5.2	NUMBER OF PATIENTS WHO CLAIMED WARFARIN PRESCRIPTIONS ACCORDING TO GENDER	114
4.5.3	FREQUENCY OF WARFARIN MEDICINE ITEMS CLAIMED ACCORDING TO GENDER.....	116
4.6	PRESCRIBING PATTERNS OF WARFARIN ACCORDING TO THE PRESCRIBED DAILY DOSE.....	118
4.6.1	THE PDD OF WARFARIN ACCORDING TO PRESCRIBERS	119
4.6.2	PDD OF WARFARIN ACCORDING TO GENDER.....	120
4.6.3	PDD OF WARFARIN ACCORDING TO AGE GROUP	121
4.7	DRUGS CO-PRESCRIBED WITH WARFARIN ACCORDING TO THE DATABASE AND THE SIGNIFICANCE RATINGS OF THESE DRUGS	123
4.7.1	GENERAL PRESCRIBING PATTERNS OF CO-PRESCRIBED DRUGS	123
4.7.2	CO-PRESCRIBED DRUGS WITH A SIGNIFICANCE RATING OF 1.....	124
4.7.3	CO-PRESCRIBED DRUGS WITH A SIGNIFICANCE RATING OF 2.....	125
4.7.4	CO-PRESCRIBED DRUGS WITH A SIGNIFICANCE RATING OF 4 AND 5	127
4.7.5	TOP 5 DRUGS CO-PRESCRIBED WITH WARFARIN	128
4.7.5.1	<i>Aspirin</i>	130
4.7.5.2	<i>Thyroxine</i>	133
4.7.5.3	<i>Amiodarone</i>	136
4.7.5.4	<i>Simvastatin</i>	139
4.7.5.5	<i>Celecoxib</i>	142
4.8	CHAPTER SUMMARY	144

CHAPTER 5: CONCLUSION AND RECOMMENDATIONS.....146

- 5.1 CONCLUSIONS..... 146**
 - 5.1.1 CONCLUSIONS BASED ON THE LITERATURE REVIEW 146
 - 5.1.2 CONCLUSIONS BASED ON THE EMPIRICAL INVESTIGATION..... 149
- 5.2 RECOMMENDATIONS..... 154**
- 5.3 LIMITATIONS 155**
- 5.4 CHAPTER SUMMARY 155**

LIST OF TABLES

Table 2.1: Compounds incompatible with solutions of warfarin sodium.....	11
Table 2.2: Drugs metabolised by the P450 system that influence the metabolism of S-warfarin and the P450 enzyme subtypes involved in their metabolism	16
Table 2.3: The P450 enzyme subtypes that catalyse both S-warfarin and R-warfarin and the different metabolites that result from them	19
Table 2.4: Drugs metabolised by the P450 system that influence the metabolism of R-warfarin and the P450 enzyme subtypes involved in their metabolism	20
Table 2.5: Summary of the hydroxywarfarins that are substrates for the glucuronidation in humans and the UGT-isoforms involved in their glucuronidation.	24
Table 2.6: The UGT-isoforms involved in the phase II metabolism of warfarin and the other compounds which they metabolise	26
Table 2.7: Example of the table in the warfarin label to predict the individual dose of warfarin based on clinical an genetic factors	29
Table 2.8: Blood clotting factors.....	32
Table 2.9: The three different groups of bleeding and their examples.....	35
Table 2.10: An example of a warfarin dosing nomogram.....	42
Table 2.11: An example of a warfarin dosing nomogram and suggested dose adjustments to achieve the desired INR.....	42
Table 2.12: The difference in the daily dose of warfarin between age groups and between males and females in an elderly population	50
Table 2.13: The enzymes invloved in the metabolism of warfarin and the drugs that induce these enzymes.....	57
Table 2.14: The enzymes involved inthe metabolism of warfarin and the drugs that inhibit these enzymes.....	58
Table 2.15: A list of all the inducers and inhibitors of P-glycoprotein	61
Table 2.16: Significance ratings of drug interactions defined by their severity and documentation level	66
Table 2.17: A list of all the drugs that potentially interact with warfarin and the assigned significance ratings of these interactions.....	67
Table 2.18: All the drugs that have a potential interaction with warfarin and the significance ratings of these drugs as adapted from Hansten & Horn (2011)	71

Table 3.1: Symbols used in the calculations of samples and population measures...	93
Table 4.1: General prescribing patterns (2005-2010).....	101
Table 4.2: Average number of prescriptions per patient and number of medicine items per prescription for the total database (2005-2010).....	101
Table 4.3: General prescribing patterns of warfarin prescriptions and warfarin medicine items for the total database (2005-2010).....	102
Table 4.4: Average number of warfarin prescriptions per patient per year and warfarin medicine items per prescription for the whole database (2005-2010).....	103
Table 4.5: Number of patients on the total database (2005-2010).....	104
Table 4.6: Trade names of warfarin products used.....	105
Table 4.7: Prescribing patterns of the different warfarin products according to different prescribers.....	106
Table 4.8: Number of warfarin prescriptions according to age group.....	108
Table 4.9: The average number of warfarin prescriptions per patient according to age group	110
Table 4.10: Average number of warfarin medicine items per warfarin prescription according to age group.....	112
Table 4.11: Number of warfarin prescriptions according to gender.....	114
Table 4.12: Average number of warfarin prescriptions per patient according to gender.....	116
Table 4.13: Number of warfarin medicine items according to gender.....	118
Table 4.14: Average PDD of warfarin according to prescribing physician.....	119
Table 4.15: Average PDD of warfarin according to gender for the whole database (2005-2010).....	120
Table 4.16: The d-values for the average PDD of age groups 1, 2, and 3 compared to age group 4.....	121
Table 4.17: Average PDD of warfarin according to age group.....	122
Table A1.1: Number of prescriptions per age group for the total database (2005-2010).....	174
Table A1.2: Number of medicine items claimed per age group for the total database (2005-2010).....	175
Table A1.3: Average number of patients per age group for the total database (2005-2010).....	176

Table A1.4: Number of prescriptions according to gender for the total database (2005-2010)	177
Table A1.5: Number of medicine items claimed per gender for the total database (2005-2010)	178
Table A1.6: The average number of prescriptions per patient according to gender for the total database (2005-2010)	179
Table A1.7: The frequency and significance rating of the drugs co-prescribed with warfarin for the total database (2005-2010)	180
Table A1.8: Frequency and significance rating of drugs co-prescribed with warfarin according to age group	180
Table A1.9: Frequency of the top 10 co-prescribed drugs with a significance rating of 1	180
Table A1.10: Frequency of warfarin co-prescribed drugs with a significance rating of 1	181
Table 1.11: Frequency of warfarin co-prescribed drugs with a significance rating of 2	182
Table A1.12: Frequency of the top 10 warfarin co-prescribed drugs with a significance rating of 2	184
Table A1.13: Frequency of warfarin co-prescribed drugs with a significance rating of 4 and 5	184
Table A1.14: The top 10 drugs co-prescribed with warfarin	184
Table A1.15: The top 5 drugs co-prescribed with warfarin	185
Table A1.16: The frequency of different aspirin doses	185
Table A1.17: Comparison of the frequencies of different warfarin doses and high risk aspirin doses	185
Table A1.18: Frequency of high risk aspirin doses according to age group	186
Table A1.19: Summary of the effects of aspirin when co-prescribed with warfarin ...	187
Table A1.20: The frequency of different thyroxine doses	188
Table A1.21: Comparison of the frequencies of different warfarin doses and thyroxine doses	188
Table A1.22: Frequency of thyroxine doses according to age group	189
Table A1.22: Frequency of thyroxine doses according to age group (continued)	190
Table A1.23: Summary of the effects of thyroxine when co-prescribed with warfarin	191
Table A1.24: Frequency of different amiodarone doses	192
Table A1.25: Comparison of the frequencies of different warfarin doses and high risk amiodarone doses	192

Table A1.26: Frequency of high risk amiodarone doses according to age group.....	193
Table A1.27: Summary of the effects of amiodarone when co-prescribed with warfarin.....	194
Table A1.28: The frequency of different simvastatin doses.....	195
Table A1.29: Comparison of the frequencies of different warfarin doses and simvastatin doses.....	195
Table A1.30: Frequency of simvastatin doses according to age group.....	196
Table A1.31: Summary of the effects of simvastatin when co-prescribed with warfarin.....	197
Table A1.32: The frequency of different celecoxib doses.....	198
Table A1.33: Comparison of the frequencies of different warfarin doses and celecoxib doses.....	198
Table A1.34: Frequency of celecoxib doses according to age group.....	199
Table A1.35: Summary of the effects of celecoxib when co-prescribed with warfarin.....	200

LIST OF FIGURES

Figure 2.1: Summary of all the metabolites formed from the metabolism of S-warfarin and the enzymes involved in this	15
Figure 2.2: The major sites of hydroxylation of S-warfarin catalyzed by CYP450 to produce hydroxylated metabolites	15
Figure 2.3: Illustration of <i>trans</i>- and <i>cis</i>-dehydrowarfarin, which is formed from the metabolism of S-warfarin by CYP3A4.....	16
Figure 2.4: Summary of all the metabolites formed from the metabolism of R-warfarin and the enzymes involved in this metabolism	18
Figure 2.5: The major sites of hydroxylation of R-warfarin catalysed by CYP450 to produce hydroxylated metabolites	19
Figure 2.6: A schematic representation of warfarin and the acetyl side chain which is reduced by the NADPH-dependent carbonyl reductase.....	22
Figure 2.7: Illustration of the sites on the hydroxywarfarin molecule where glucuronidation takes place.....	25
Figure 2.8: The vitamin K cycle and the sites of action of VKOR	28
Figure 2.9: The coagulation cascade.....	32
Figure 2.10: The link between the vitamin K cycle and the γ-carboxylation of glutamate residues	34

Figure 2.11: Schematic representation of the mechanisms of drug interactions

52Figure 2.12: A broad classification of current and new anticoagulants with the trade names of those anticoagulants currently on the South African market 74

Figure 2.13: Platelet aggregation and the sites of action of antiplatelet drugs 78

Figure 2.14: The complete coagulation cascade and the sites of action of the anticoagulants currently available on the local market 81

Figure 3.1: Graphical representation of the data analysis process..... 92

Figure 4.1: Organogram of the empirical investigation..... 99

LIST OF GRAPHS

<i>Graph 4.1: The PDD of warfarin according to prescribing physicians.....</i>	120
<i>Graph 4.2: PDD of warfarin according to gender.....</i>	121
<i>Graph 4.3: The PDD of warfarin according to age group for the total database (2005-2010)</i>	122
<i>Graph 4.4: Number of and significance ratings of drugs co-prescribed with warfarin</i>	123
<i>Graph 4.5: The frequency and significance ratings of drugs co-prescribed with warfarin according to age group.....</i>	124
<i>Graph 4.6: The top 10 drugs co-prescribed with warfarin with a significance rating of 1</i>	125
<i>Graph 4.7: Frequency of warfarin co-prescribed drugs with a significance rating of 2</i>	126
<i>Graph 4.8: The top 10 drugs co-prescribed with warfarin with a significance rating of 2</i>	126
<i>Graph 4.9: Frequencies of warfarin co-prescribed drugs with a significance rating of 4 and 5</i>	128
<i>Graph 4.10: The top 10 drugs co-prescribed with warfarin.....</i>	129
<i>Graph 4.11: The top 5 drugs co-prescribed with warfarin.....</i>	130
<i>Graph 4.12: The frequency of different ranges of aspirin doses</i>	131

Graph 4.13: Comparison of the frequencies of different warfarin doses and high risk aspirin dose ranges	132
Graph 4.14: High risk aspirin doses according to age group	133
Graph 4.15: The frequency of different thyroxine doses.....	134
Graph 4.16: Comparison of the frequencies of different warfarin doses and different thyroxine dose ranges.....	135
Graph 4.17: Dose ranges of thyroxine according to age group.....	135
Graph 4.18: The frequency of different amiodarone doses	137
Graph 4.19: Comparison of the frequencies of different warfarin doses and high risk amiodarone dose ranges.....	138
Graph 4.20: High risk amiodarone doses according to age group.....	139
Graph 4.21: The frequency of different simvastatin doses	140
Graph 4.22: Comparison of the frequencies of different warfarin doses and simvastatin dose ranges.	141
Graph 4.23: Simvastatin doses according to age group.....	141
Graph 4.24: The frequency of different celecoxib doses	142
Graph 4.25: Comparison of the frequencies of different warfarin doses and celecoxib dose ranges.....	143
Graph 4.26: Celecoxib doses according to age group	144
Graph A1.1: Frequency of warfarin co-prescribed drugs with a significance rating of 1	183

ACKNOWLEDGEMENTS

I want to extend my sincerest gratitude to all the people who were involved in this study and who supported me throughout this journey.

- ❖ I would firstly like to thank my family Frans, Huipie and Lizelle Blaauw, Chrisna, André, and little Stephan Huisamen for all of their love and unending support. I would have certainly not been able to do this without your love, guidance and encouragement. I love you very much.
- ❖ I would like to thank the three best friends in the world Cecilia Swart, Lindi van Zyl and Deon du Plessis for their friendship, support, guidance, and most of all fun and laughter throughout my university career.
- ❖ Dr Rianda Joubert in her capacity as study supervisor for all her help, knowledge, and encouragement throughout this study.
- ❖ Prof Martie Lubbe in her capacity as co-supervisor for all her help and encouragement in the data analysis and her unending knowledge in this field.
- ❖ Dr Johan Lamprecht in his capacity as co-supervisor for his input in this study.
- ❖ Miss Anne-Marie Bekker for her support in the data analysis process. I will never forget the support, advice, hours of chatting and laughter. Thank you very much!
- ❖ Mrs. Engela Oosthuizen for always lending an ear and a shoulder to cry on whenever I needed it and for all the cup-cakes and cups of coffee. Thank you very much!
- ❖ To my fellow M-students Christelle Coetzer, Dana Le Roux and Hannes De Wet for your friendship, fun and laughter. It was a pleasure working with you.
- ❖ Mrs Helena Hoffman for her technical support.

ABSTRACT

Title: Prevalence of drug-drug interactions of warfarin prescriptions in South Africa.

Keywords: Warfarin, drug-drug interactions, anticoagulant, vitamin K antagonist, drug utilisation review, private health care sector, prescribed daily dose (PDD), pharmaceutical benefit management company.

Background: Warfarin is an anticoagulant that is used for the prophylactic and therapeutic treatment for a wide range of thrombo-embolic disorders. The prescribing and monitoring of warfarin therapy is challenging due to the fact that warfarin exhibits numerous interactions with other drugs and a variety of factors that influence the dosing of warfarin.

Objective: The general objective of this study was to investigate the prevalence of drugs prescribed with warfarin that may have a potential drug-drug interaction (DDI) with warfarin.

Methods: This was a cross-sectional, observational or qualitative study that was conducted on medicine claims data of a pharmaceutical benefit management company for patients receiving warfarin therapy for a six year period, ranging from 1 January 2005 to 31 December 2010. Drug products that were co-prescribed with warfarin were also identified from the medicine claims database. The total number of prescriptions for all drug products during the study period were analysed and compared to the warfarin dataset. This was done by means of the SAS 9.1[®] computer package (SAS Institute, 2004). The total number of prescriptions and medicine items claimed from the database during the study period were respectively 49 523 818 and 118 305 941. Potential DDIs between warfarin and co-prescribed drugs were identified and classified according to a clinically significant rating. The clinical significance ratings of potential DDIs are described in three degrees of severity, identified as major, moderate and minor (Tatro, 2011:xiv).

Results: The database consisted of 427 238 warfarin prescriptions and 427 744 warfarin medicine items, which represented 0.9% of the total number of prescriptions and 0.4% of total number of medicine items. The total number of patients who claimed warfarin prescriptions through the database represented 0.9% (n=68 575) of the total number of patients who claimed prescriptions in the total database (2005-2010). General practitioners prescribed the highest frequency of warfarin medicine items, representing 58.3% (n=249 202) of the total number prescribed. The age group that claimed the highest

frequency of warfarin prescriptions (n=327 592, 76.6%) and the highest frequency of warfarin medicine items (n=327 984, 76.7%) was age group 4 (consisting of patients 59 years and older). The distribution between females and males regarding warfarin prescriptions claimed (n=205 999, 48.2%; n=221 117, 51.8%) and warfarin medicine items claimed (n=206 232, 48.2%; n=221 390, 51.8%) were almost equal. General practitioners prescribed the highest average PDD (7.01 mg ± 9.86 mg) of warfarin medicine items. Paediatric cardiologists prescribed the lowest average PDD (4.61 mg ± 1.29 mg) of warfarin medicine items. A d-value of 0.1 indicates that there is no practical difference of the average PDD between general practitioners and paediatric cardiologists. The average PDD of warfarin medicine items between females (6.60 mg ± 9.06 mg) and males (6.74 mg ± 8.41 mg) was almost equal. The age group who was prescribed the highest average PDD was age group 2 (consisting of patients 20 years to 39 years old) (7.42 mg ± 7.42 mg). Age group 4 (consisting of patients 59 years and older) (6.50 mg ± 8.90 mg) was prescribed the lowest average PDD of warfarin medicine items. A d-value of 0.1 indicates that there is no practical difference of the average PDDs of warfarin medicine items between these two age groups.

The results revealed that drugs with a significance rating (SR) of 1 (n=155 066, 43.3%), 2 (n=30 128, 8.4%), 4 (n=137 144, 38.3%), and 5 (n=36 144, 10.1%) were co-prescribed with warfarin in the six year study period. The five drugs that was co-prescribed with warfarin most frequently was aspirin (n=48 903, 13.6%), thyroxine (n=33 954, 9.5%), amiodarone (n=25 056, 7.0%), simvastatin (n=19 070, 5.3%) and celecoxib (n=10 794, 3.0%). These five drugs have a SR of 1.

Conclusions: This study showed that the top five drugs most frequently prescribed with warfarin are aspirin, thyroxine, amiodarone, simvastatin and celecoxib. These drugs can potentially interact with warfarin. The potential interactions of these drugs are rated with a significance rating of 1. This concludes that drugs that can potentially cause life threatening effects and permanent damage are commonly co-prescribed with warfarin. Clinical data concerning the INR or PT must be obtained in order to evaluate whether or not warfarin therapy is changed when a potentially interacting drug is co-prescribed. The age of the patients as well as the duration of warfarin treatment should also be obtained in order to assess whether warfarin treatment is changed with the progression of age.

OPSOMMING

Titel: Voorkoms van geneesmiddelinteraksies op warfarien voorskrifte in Suid-Afrika

Sleutelwoorde: Warfarien, geneesmiddel-geneesmiddelinteraksies (GGI), antikoagulante, vitamien K antagonist, medisyneverbruiksevaluering, private gesondheidsorgsektor, voorgeskrewe daaglikse dosering (VDD), farmaseutiese voordele bestuursmaatkappy.

Agtergrond: Warfarien is 'n antikoagulant wat gebruik word vir die profilaktiese en terapeutiese behandeling van 'n wye verskeidenheid trombo-emboliese toestande. Die voorskryf en kontrolering van warfarinterapie is uitdagend vanweë die feit dat warfarien verskeie interaksies met ander geneesmiddels kan hê en 'n wye verskeidenheid van faktore die dosering van warfarien beïnvloed.

Doelwit: Die algemene doelwit van die studie is om die voorkoms van moontlike interaksies met geneesmiddels wat saam met warfarien voorgeskryf word te ondersoek.

Metodes: 'n Deursnee-, waarnemings- of kwalitatiewe studie is onderneem met betrekking tot die medisyne-eisdata van 'n farmaseutiese voordele bestuursmaatskappy vir pasiënte wat warfarientherapie ontvang het tydens 'n ses jaar periode vanaf 1 Januarie 2005 tot 31 Desember 2010. Geneesmiddels wat saam met warfarien voorgeskryf is is ook uit die medisyne-eisdatabasis geïdentifiseer. Die totale hoeveelheid voorskrifte vir alle medisyne-items gedurende die studietydperk is ook geanaliseer en met die warfarien datastel vergelyk. Dit is gedoen met behulp van die SAS 9.1[®] rekenaarpakket (SAS Instituut, 2004). Die totale hoeveelheid voorskrifte en medisyne-items wat ge-eis is vanaf die databasis gedurende die studietydperk was onderskeidelik 49 523 818 en 118 305 941. Potensiële GGI tussen warfarien en mede-voorskrewe geneesmiddels is geïdentifiseer en geklassifiseer met 'n kliniese beduidende gradering. Die kliniese beduidende graderings of potensiële GGI is beskryf na gelang van drie grade van erns naamlik belangrik, gemiddeld en onbelangrik (Tatro, 2011:xiv).

Resultate: Die databasis het 427 238 warfarien voorskrifte en 427 744 warfarien medisyne-items opgelewer, wat 0.9% van die totale hoeveelheid voorskrifte verteenwoordig het, en 0.4% van die totale hoeveelheid medisyne-items. Die totale hoeveelheid pasiënte wat warfarien voorskrifte deur die databasis ge-eis het verteenwoordig 0.9% (n=68 575) van die

totale hoeveelheid pasiënte wat voorskrifte ge-eis het in die totale databasis (2005-2010). Algemene praktisyns het die meeste warfarië medisyne-items voorgeskryf, naamlik 58.3% (n=249 202) van die totaal. Die ouderdomsgroep wat die meeste warfarië voorskrifte ge-eis het (n=327 592, 76.6%) en die meeste warfarië medisyne-items ge-eis het (n=327 984, 76.7%) is ouderdomsgroep 4 (bestaande uit pasiënte 59 jaar en ouer). Die verspreiding tussen vroue en mans met betrekking tot die warfarië voorskrifte wat ge-eis is (n=205 999, 48.2%; n=221 117, 51.8%) en die warfarië medisyne-items wat ge-eis is (n=206 232, 48.2%; n=221 390, 51.8%) was byna dieselfde. Algemene praktisyns het die hoogste gemiddelde VDD (7.01 ± 9.86) van warfarië geneesitems voorgeskryf. Pediatrisie kardioloë het die laagste gemiddelde VDD (4.61 ± 1.29) van warfarin medisyne-items gehad. 'n D-waarde van 0.1 dui aan dat daar geen praktiese verskil is met betrekking tot die gemiddelde VDD tussen algemene praktisyns en pediatrisie kardioloë nie. Die gemiddelde VDD van warfarië medisyneitems tussen vroue (6.60 ± 9.06) en mans (6.74 ± 8.41) was byna gelyk. Die ouderdomsgroep wat die hoogste gemiddelde VDD gehad het was ouderdomsgroep 2 (7.42 ± 7.42). Ouderdomsgroep 4 (6.50 ± 8.90) het die laagste gemiddelde VDD van warfarië medisyne-items ge-eis. 'n D-waarde van 0.1 dui geen praktiese betekenisvolle verskil in die gemiddelde VDD's van warfarië medisyne-items tussen hierdie twee ouderdomsgroepe nie.

Die resultate het getoon dat geneesmiddels met 'n beduidendheidsgradering (BG) van 1 (n=155 066, 43.3%), 2 (n=30 128, 8.4%), 4 (n=137 144, 38.3%), en 5 (n=36 144, 10.1%) saam met warfarië voorgeskryf is gedurende die ses jaar periode. Die vyf geneesmiddels wat saam met warfarië voorgeskryf is sluit in aspirien (n=48 903, 13.6%), tiroksien (n=33 954, 9.5%), amiodaroon (n=25 056, 7.0%), simvastatien (n=19 070, 5.3%) en celecoxib (n=10 794, 3.0%). Hierdie vyf middels het elk 'n BG van 1.

Gevolgtrekkings: Hierdie studie het gewys dat die vyf geneesmiddels wat die meeste saam met warfarië voorgeskryf is die volgende insluit: aspirien, tiroksien, amiodaroon, simvastatien en celecoxib. Hierdie geneesmiddels kan potensieel met warfarië reageer, met 'n potensieël interaksiegradering met 'n beduidendheid van 1. Dit beteken dat geneesmiddels wat potensieel lewensbedreigende effekte of permanente skade kan doen algemeen saam met warfarin voorgeskryf word. Kliniese data met betrekking tot die Internasionale Genormaliseerde Verhouding of protrombientyd moet bekom word om te evalueer of warfarientherapie aangepas word wanneer 'n geneesmiddel wat 'n potensieël interaksie met warfarië het, saam met warfarië voorgeskryf word. Die ouderdom van die pasiënt en die duur van warfarientherapie moet ook bekom word om te assesser of warfarië terapie aangepas word soos wat die pasiënt ouer word.