

Prevalence of Warfarin Drug Interaction and Warfarin Education Practice in Outpatient Setups of University Teaching Hospital

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ABSTRACT

Introduction: Pharmacokinetic, pharmacodynamic and narrow therapeutic index properties of warfarin makes it particularly susceptible to interactions with a number of prescription and nonprescription drugs, including dietary supplements and herbal medicines. Patients requiring warfarin should then be educated with respect to the therapy safety and effectiveness issues as this improves patient's knowledge and quality of anticoagulation. **Objective:** To assess the prevalence of warfarin drug interaction (WDI) and its dispensing practice at outpatient departments (OPD) of Tikur Anbessa Specialized Hospital (TASH). **Methods:** A cross sectional study was carried out in 360 adult outpatients whom warfarin was prescribed for various indications at cardiac and hematology clinics (CHCs) by reviewing their chart retrospectively. To assess warfarin dispensing practice at outpatient pharmacies of the hospital, direct observation using checklist was conducted towards pharmacy professionals' services provision to patients regarding warfarin therapy. Micromedex online database was used to analyze drug interaction. **Results:** Out of 360 study participants nearly two third (64.7%) of them were female patients. A total of 76 (21.1%)

WDIs were identified in this study. Moderate type of interaction accounted for 75.4% and the remaining was major type of interactions. Among the identified warfarin related education practice, the highest points were on educating patients on their daily dose, when to take warfarin and telling them the name of drug they receive as such education were given to 74.1%, 67% and 59.8% of patients respectively. From the total of 112 of the actual warfarin dispensed to the patients, only 45 (40.2%) were labeled with how to receive the drug. **Conclusion:** Prevalence of warfarin drug interaction was minimal among outpatients of CHCs of TASH. Warfarin dispensing practice at outpatient pharmacies of the hospital was not optimal.

Key words: Warfarin drug interaction, warfarin education, warfarin counseling tips

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INTRODUCTION

The use of oral anticoagulants for treatment and prevention of thromboembolic (TE) diseases in clinical practice began in the 1920s.^[1] Among these, the vitamin K antagonist (warfarin), has been used widely for this purpose effectively for more than six decades with well-established evidences.^[2,3] Warfarin exerts its anticoagulant effect by interfering with the hepatic synthesis of vitamin K-dependent clotting factors II, VII, IX, and X and proteins C and S.^[4] Warfarin is used for a variety of indications^[5,6] including, prevention and treatment of venous thromboembolism (VTE), in patients with prosthetic heart valves^[7-9], stroke^[10], stroke prevention in atrial fibrillation patients, in patients with markedly depressed left ventricular ejection fraction, left ventricular aneurysm, etc.^[11] Warfarin is well absorbed from gastrointestinal tract, highly bound to the plasma proteins (99%) and is metabolized via the cytochrome P450 system.^[12] The clinical significance and intensity of warfarin interactions with prescription drugs can often be predicted on the basis of known metabolic characteristics of the drugs and warfarin enantiomers.^[4] Pharmacokinetic and pharmacodynamic properties of warfarin and its narrow therapeutic index properties make it particularly susceptible to interactions with other prescription and nonprescription drugs, including dietary supplements and herbal medicines.^[9] In patients taking warfarin, the introduction of agents that increase/decrease hepatic microsomal enzymes/clotting factors synthesis/catabolism, may affect the risk of TE and hemorrhagic complications.^[4] Interactions between warfarin and agents that inhibit platelet aggregation can increase the risk of bleeding without affecting the prothrombin time.^[13]

Patients requiring warfarin should be educated with respect to the

therapy safety and effectiveness issues so as to improve patients' knowledge and quality of anticoagulation. Healthcare providers should counsel patients receiving warfarin on what warfarin is, how the medication works, about common side effects, the need frequent INR monitoring, precautionary measures to decrease trauma or bleeding, what to do if there are miss doses, on potential drug-drug, drug-herbals, drug-food (vitamin K enrich diet) and drug-alcohol interaction.^[14-17] However, relatively little attention appears to have been taken to the development of robust models of patient education in the setting of oral anticoagulant therapy.^[18] To best of our knowledge, no research has been conducted in Ethiopia regarding warfarin drug interaction in outpatient clinics and assessed observationally counseling practice of pharmacists to patients receiving warfarin using prospective observation. Therefore, our study was to assess the prevalence of warfarin drug interaction in outpatients department (OPD) of cardiac and hematology clinics (CHCs) and warfarin education practice in outpatient pharmacies of Tikur Anbessa Specialized Hospital (TASH), Addis Ababa, Ethiopia.

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MATERIALS AND METHODS

Study setting

The study was conducted at TASH which is found at Addis Ababa, Ethiopia. TASH is the largest tertiary university teaching hospital in the country where warfarin is prescribed and dispensed widely for various indications.

Study design

A cross sectional study design in which retrospective patients' charts review was used to collect patients' data from outpatients whom warfarin was prescribed for its various indication in CHCs of TASH. To assess warfarin dispensing practice at outpatient pharmacies of the hospital, direct observation using checklist was conducted to the services pharmacy professionals were providing to patients regarding warfarin therapy was observed.

Sampling and study participants' selection

The charts of all patients age 18 and above years, on warfarin for at least 3 months, attending CHCs of TASH during the period of January 2011 to January 2012 were enrolled in the study. Accordingly, 360 patients' charts were included and during the review process demographic (age, sex) and clinical characteristics (indications of warfarin, warfarin dose per day, drugs prescribed concurrently with warfarin) were collected using the structured data collection which was validated by clinical pharmacist and consultant cardiologist. Standardized checklist was used to assess warfarin dispensing and counseling practice at outpatient pharmacies of the TASH. Accordingly, 112 counseling practice of pharmacy professionals on warfarin were observed at two outpatient pharmacies of the hospital from June 3 to 14, 2012.

Data collection and management

Drug interaction level is classified as follows based on the severity.^[19,20] Contraindicated: The interaction may serve as a reason to withhold the medical treatment due to the harmful effect that it would cause to the patient. Major drug interaction: The interaction may be life-threatening and/or require medical intervention to minimize or prevent serious. Moderate drug interaction: The interaction may result in exacerbation of the patient's condition and/or require an alteration in therapy adverse effects. Minor drug interaction: A type interaction that would have limited clinical effects which would not require a major alteration in therapy.

The observation checklist was developed from published literatures.^[12,21,22] Then, it was adopted as it can be suitable to the study setup to collect information regarding warfarin counseling practice provided by pharmacists at the outpatient pharmacies on: the name of drug they are receiving, indication of warfarin, dose of warfarin per day, the best time to take warfarin, the probable interaction between warfarin and concurrent prescribed drugs/over the counters/herbal medicines, intake of green leafy vegetables, alcohol consumption, information related to side effects of warfarin, what to do on missed warfarin dose and labeling of dispensed warfarin, presence of warfarin counseling room, availability of registration for dispensed warfarin prescriptions per day).

Data analysis

Micromedex online database was used to analyze drug interaction between warfarin and other drug prescribed for patients.^[19] WDIs data was collected by four pharmacists after they were given training on how to extract the required information from patients' charts. Similarly, for assessing warfarin dispensing and counseling practice four pharmacy technicians were recruited and allowed to collect the necessary information by observing pharmacy professionals on

warfarin dispensing and counseling practice. The data obtained from both techniques were entered into a computer using Epi Info version 3.5.3 and analyzed by SPSS version 20.

Ethical consideration

Ethical clearance was obtained from the ethical review committee of School of Pharmacy, College of Health Sciences, Addis Ababa University. Then, official support letter was written by Department of Pharmacology and Clinical Pharmacy to TASH and permission was obtained from the hospital in which the study was carried out. Information obtained from all data collection in the course of study was only handled by the research team; the study doesn't intend to disclose individual names or identity.

RESULTS

Socio-demographic and clinical characteristics

Out of 360 study participants, nearly two-thirds of (64.7%) were female patients [Table 1]. The mean daily dose of warfarin was 5.1 mg (SD=2.24) with the minimum and maximum doses of 1.5 and 18.4 mg, respectively.

Prevalence of warfarin drug interactions

A total of 76 (21.1%) WDIs were identified in this study using Micromedex online drug reference analysis. Moderate type of interaction was accounted for 75.4% of the total drug interactions and the remaining were the major type of interactions. Propranolol 24.7 (6.7%), and omeprazole 10 (2.8%) were among the most frequent drugs interacted with warfarin. The contribution of other remaining drugs was few to the interactions as they were prescribed only 1 to 5 times. There were no drugs which have minor interaction and absolute contraindication with warfarin in our study [Table 2].

Warfarin education practice at outpatients pharmacies

Among the identified warfarin related counseling or dispensing practice, the highest points were on informing patients the name of drug; the daily dose of warfarin by each patient and when to take warfarin as such education were given to 49.8%, 74.1 and 67% of patients respectively. From the total of 112 of actually warfarin dispensing practice, only 45 (40.2%) were labeled on how to receive the drug. The remaining counseling points on warfarin therapy by pharmacy professionals were provided to few patients [Table 3]. During the study period, outpatient pharmacies had no separate warfarin counseling room and didn't register dispensed warfarin prescription by patient, dose, etc.

DISCUSSION

This study attempted to assess indications of warfarin; prevalence and level of WDIs among outpatients who were on follow up at CHC of the hospital; and counseling service provided by pharmacists for patients receiving warfarin from outpatient pharmacies of the hospital the mean age of our study participants was only 35.3 (SD=12.8) years, which was almost two times lower than report from The United States and Canada studies^[2,23-26] and similarly higher mean age was recorded in patients receiving warfarin in Sweden.^[27] The difference may be due to our patients had been on warfarin since few years as compared with developed countries patients who received the drug for decades of their life. The daily dose of warfarin in this study was almost similar with figures reported elsewhere.^[25,28]

The prevalence of WDI was minimal (21.1%) in our study. In contrary to this, study done in acute care admissions of San Francisco Veterans Affairs Medical Center reported more than 100% WDI^[24] and also in Ayder Referral Hospital, Northern Ethiopia extremely high rate (99.2%)

Tadesse TA, *et al.*: Prevalence of Warfarin Drug Interaction and Warfarin Education Practice in Outpatient Setups of University Teaching Hospital: A Retrospective Chart Review and an Observational Study

of WDI was identified in the inpatient set up of the hospital. Out of the total, three fourth of interactions were moderate types, and it is almost similar to Ethiopian study. The lower prevalence of WDI in our study may be because of outpatients requiring less intensive management protocol as compared to inpatients. Furthermore, outpatients usually have few co-morbidities requiring less polypharmacy as they are relatively stabilized in which many interventions were made to optimize treatment outcome.^[28]

In the present study, all drugs found to interact with warfarin are known to increase warfarin effect (increasing risk of bleeding) by inhibition liver enzymes which metabolize warfarin except carbamazepine and phenobarbitone which decrease the effect of warfarin (increasing risk of thromboembolism) even if phenytoin has biphasic effect on warfarin action.^[12] However, both type effects were widely reported in other studies.^[3,28,29] The most common WDIs were noticed from antibiotics which are in agreement with other previous studies reports^[28] and then comparable interaction from statin, anticonvulsants and gastrointestinal drugs. Prescribers should understand severity and outcome of WDIs as such bad practice may result in treatment ineffectiveness or over anticoagulation and bleeding risk.^[12] We haven't assessed such clinical significance in this study since the patients were on long follow up and difficult to obtain such outcomes (reports from patients, emergency visits, adverse drug reaction, etc.) from their charts.

Effective patient counseling/education regarding their medications is an essential component of medication safety as it improves patients' knowledge of their disease and how to manage their drug therapy.^[14] This is essential in the quality management of the anticoagulated patient.^[30] In this we tried to assess the dispensing and counseling of pharmacy professionals at outpatients pharmacies of the hospital regarding warfarin. The name of the drug patients was receiving; and indication of warfarin was told to only 59.8% and 37.5% of study participants respectively. However, many studies stated that basics of anticoagulation education should include informing the patients the name of the drug, mechanism of action of warfarin action and its clinical indication.^[22,30] In this observational study, only 67% of patients were counseled on when to receive their warfarin which should have been 100% unless the patient may take their drug at any time of the day which might affect the optimal treatment outcome and level of their adherence to the treatment.^[31] In our study, only one-tenth of patients

were provided information on what to do if they missed their warfarin daily dose. The recommendation is if remembered on the same day, it should be taken right away at the prescribed dose. If remembered only the next day, the patients should not receive the dose from the previous day, only the dose for that day.^[14,31]

Education provided by pharmacists on the importance of interaction between warfarin and prescription only drug/ and over the counter drugs/was very suboptimal as such information was delivered to 9% and 4.5% of patients. The metabolism of warfarin allows for both pharmacokinetic and pharmacodynamic mechanisms (induction or inhibition of cytochrome P450 isozymes displacement of binding with plasma proteins, alterations in vitamin K status and contribution of hemorrhagic or thrombotic risk) of drug interaction^[12] which predispose it to interact with many concurrently used drugs. Such potential interactions between warfarin and other drugs may result in increased risk of bleeding or thromboembolism and/or affect International Normalized Ratio (INR) reading.^[32] Based on level and outcome of interactions, pharmacy professionals shall inform patients and their prescribers on the importance of monitoring INR closely (when starting or stopping interacting drug) and more frequently, decreasing/increasing dose of concurrent drug or warfarin, stopping(avoiding) interacting drug and replacing with others.^[12]

Only 17% of patients received education from pharmacists on how to take/limit green leafy vegetables while they are on warfarin therapy. A generous or poor intake of food rich in vitamin K can interact with warfarin to result in sub-therapeutic anticoagulation or life-threatening hemorrhagic complications. Thus, the need for healthcare professionals to counsel their patients on these relationships is very crucial.^[33] Informing patients the possible side effects (bleeding and clotting) they may face while receiving warfarin is important as warfarin-related bleeding continues to place a significant burden on healthcare systems worldwide and devastating to individuals.^[22] In this regard, only very few patients received education from pharmacists in outpatients pharmacies of the hospital in our study [Table 3]. In our study, labeling practice of dispensed warfarin at outpatient pharmacies was poor as only in 40.2% of patients' drug had adequate label on it which is significantly different from the ideal value of 100%. During the study period, the hospital didn't have private counseling room for patients receiving drugs (*e.g.*, warfarin) for chronic illness and they

Table 1: Socio-demographic and clinical characteristics of outpatients who were on warfarin (N=360)

Item Description	N (%)	
Sex	Male	127(35.3)
	Female	233(64.7)
Age (in Years)	18-30	155(43.1)
	31-45	140(38.9)
	46-60	42(11.7)
	Above 60	23(6.3)
Indication of warfarin	Atrial Fibrillation	164(45.6)
	Deep Vein Thrombosis	20(5.6)
	Pulmonary Embolism	7(1.9)
	Valvular Heart Disease	174(48.3)
	Myocardial Infarction	22(0.6)
	Atrial Valve Replacement	45(12.5)
	Mitral Valve Replacement	107(29.7)
	Bioprosthetic valve replacement	6(1.7)
Others ^a	40(11.1)	

^a Others include cardiomyopathy, dilated cardiomyopathy, cardiac embolic stroke, antiphospholipid antibody syndrome, peripheral vascular disease. The percentage of indication of warfarin couldn't be added to 100 as patients may have more than one indication which needs warfarin. NB: Some of the data in this table has been reported in the previously published article by one of the authors of this manuscript who was also the PI of the previous work as it is the continuation of it.^[23]

Tadesse TA, *et al.*: Prevalence of Warfarin Drug Interaction and Warfarin Education Practice in Outpatient Setups of University Teaching Hospital: A Retrospective Chart Review and an Observational Study

Table 2: Prevalence of warfarin drug interaction at CHCs of TASH (N=360)

Level of Interaction	Interacting drug	N (%)	Potential outcome
Major	Amoxicillin	2(0.6)	Increasing risk of bleeding
	Norfloracin	1(0.3)	
	Aspirin	1(0.3)	
	Erythromycin	3(0.8)	
	Fluconazole	1(0.3)	
	Metronidazole	1(0.3)	
	Sertaline	1(0.3)	
	Simvastatin	3(0.8)	
	Amoxicilin and clavunic acid	4(1.1)	
	Clarithromycin	2(0.6)	
Moderate	Ketoconazole	2(0.6)	Decreasing anticoagulant effectiveness
	Lovastatin	4(1.1)	
	Propranolol	24(6.7)	
	Cimetidine	2(0.6)	
	Carbamezipine	2(0.6)	
	Phenobarbitone	4(1.1)	
	Omeprazole	10(2.8)	
	Tramadol	4(1.1)	
	Phenytoin	5(1.4)	
		Increase in prothrombin time and an increased the risk of bleeding.	
		Transient increased risk of bleeding when starting phenytoin during warfarin therapy, but a decreased anticoagulant effect during continued warfarin therapy	

Table 3: Education practice regarding warfarin at outpatients pharmacies of TASH (N=112)

S.N	Item description (patient counseling/education points on warfarin)	Yes N(%)	No N (%)
1	Did pharmacists tell the patients the name of the drug?	67(59.8)	33(40.2)
2	Did pharmacists tell the patients the indication of warfarin?	42(37.5)	70(62.5)
3	Did pharmacists tell the patients the strength/dose of warfarin he/she should take per day?	83(74.1)	29(25.9)
4	Did pharmacists tell the patients when he/she take the medication?	75(67)	37(33)
5	Did pharmacists tell the patients the probable interaction between warfarin and other medication(s) he/she received from pharmacy with warfarin?	9(9)	103(92)
6	Did pharmacists advise the patients the probable interaction between warfarin and other medication(s) by asking him/her the current medication(s) he/she is taking prior to this visit?	3(2.7)	97(97.3)
7	Did pharmacists inform the patients the probable interaction between warfarin and over the counter drugs?	5(4.5)	107(95.5)
8	Did pharmacists tell the patients the probable interaction between warfarin and traditional medicines?	3(2.7)	97(97.3)
9	Did pharmacists advise the patients on how take/ limit the intake of green leafy vegetables?	19(17)	93(83)
10	Did pharmacists tell the patients on how avoid/ limit the intake of alcohol?	10(8.9)	102(91.1)
11	Did pharmacists let know the patients the side effect(s) may he/she face while taking warfarin?	2(1.8)	110(98.2)
12	Did pharmacists notify the patients how he/she recognizes warfarin side effects like bleeding and thrombosis?	1(0.9)	111(99.1)
13	Did pharmacists advise the patients on what type(s) of side effects the patient should come to the emergency room?	3(2.7)	97(97.3)
14	Did pharmacists tell the patients what to do if he/she misses the dose of warfarin?	11(9.8)	101(90.2)
15	Did pharmacists write a label on warfarin before the patient leave the pharmacy?	45(40.2)	67(59.8)
16	Did pharmacists ask the patient to reverb again on the most important points on warfarin (e.g. dosing)	12(10.7)	100(89.3)
17	Did pharmacists allow the patient to ask for unclear things regarding warfarin?	27(24.1)	85(75.9)

Tadesse TA, *et al.*: Prevalence of Warfarin Drug Interaction and Warfarin Education Practice in Outpatient Setups of University Teaching Hospital: A Retrospective Chart Review and an Observational Study

didn't register warfarin prescription.

This study had some limitation. Firstly, WDI was conducted by using retrospective chart review, we haven't assessed the outcome of interaction, the action taken by patients for possible bad outcome and intervention by their providers in case of visiting emergency room as obtaining such follow up was rare from charts. In assessing counseling practice at outpatient pharmacies in this study, we haven't included in the observation checklist points like duration of warfarin therapy, about INR (meaning significance, target and regular determination) (as they were not task of pharmacists in our hospital) and suggestion of wearing medical alert bracelet or necklace or carrying warfarin identification (since it was not applicable in the studied hospital).

CONCLUSION AND RECOMMENDATION

In this study, prevalence WDI was minimal (21.1%) among outpatients who were attending CHCs of TASH. Almost all identified drugs to interact with warfarin were those which known to increase warfarin effect (increasing risk of bleeding). Prescribers should give attention to potential drug interaction while prescribing concurrent drugs for patients receiving warfarin. Warfarin dispensing and counseling practice at outpatient pharmacies of the hospital was not optimal as most of the important counseling tips on warfarin therapy were provided to few patients. Thus, verbal and written education by pharmacists of outpatients shall be improved to enhance patients' knowledge on warfarin therapy as this is important for optimal patient outcomes of from anticoagulation. To make this effective hospital shall prepare private counseling room; prepare counseling aids and preparation and labeling materials.

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