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WARFARIN AND PRESCRIPTIONS: ASSESSMENT OF POTENTIAL INTERACTIONS IN OUTPATIENTS AGED 45 AND OLDER

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ABSTRACT

General practitioners prescribe warfarin for thromboembolic diseases prevention and treatment. Warfarin interactions with other drugs have not been systematically studied in outpatients to date. To determine whether there may be interactions between warfarin prescriptions and the rates of outpatients receiving the drug, we analyzed a cohort of outpatients receiving warfarin treatment. A retrospective study was conducted on 203,543 outpatients age 45 or older, of whom 7,074 were receiving warfarin therapy. A study analyzed patients who had taken more than one prescription medication concurrently with warfarin for at least 5 days. Stockley's Drug Interactions and domestic drug interaction databases were used to evaluate possible drug interactions in Epocrates online and Stockley's Drug Interactions. According to the study, patients taking warfarin concurrently used 4.7 drugs (SD=1.9) (males 4.7 SD=2.0, females 4.9 SD=2.0). Three-quarters of patients did not experience any interactions, 29% had at least one interaction, and 34% had two or more interactions. Men and women had about the same number of potential interactions on average. In general, there were more potential interactions with more drugs. More than half of the patients detected interactions related to warfarin, and 1 to 5 interactions were found per patient. Simvastatin (8%) and amiodarone (6%) were the drugs used most frequently with warfarin (15%). Among outpatients receiving warfarin, 58% have medications that could interact with warfarin. NSAID prescriptions account for most (15%) of interactions with warfarin.

Key Words: Warfarin, Outpatients, Prescriptions.

INTRODUCTION

Stroke and venous thromboembolism, which are increasing in frequency and severity, contribute significantly to mortality and morbidity. [1] Patients with atrial fibrillation are more likely to suffer from these conditions, and long-term treatment is ultimately necessary for these patients. [2,3] Thromboembolic disease prevention drugs are most commonly used warfarin. [4-6] Warfarin is an important anticoagulant agent because of its low cost and effectiveness and because it is available in an oral formulation. As warfarin's therapeutic index is narrow, patient compliance is unreliable, inter-individual variability is high, and it interacts with many other drugs, this drug still causes many adverse reactions/events despite its 60-year history. [7-10]

In addition to insulin and digoxin, warfarin is one of the most commonly related drugs with Complications associated with drugs that are severe.[11] Most of these interactions occur with other drugs (about 400).[12,13] The interaction between warfarin and other drugs may result in bleeding events in patients who are taking anticoagulants.[14] It has been reported that warfarin can cause theoretical (clinically insignificant) interactions as well as severe life-threatening interactions. Bleeding is one of the most frequent clinical manifestations of the interactions, ranging anywhere from superficial ecchymoses to severe hemorrhages in the gastrointestinal

tract or brain. In about 70% of warfarin interactions, its effects are increased, whereas in 15% of interactions, its effects are reduced. [15]

Adverse effects of warfarin are more often experienced by elderly patients than by younger patients. Warfarin therapy was associated with twice as many major bleeding episodes in patients over 65 as in younger patients. [10] Excessive anticoagulation is more likely to occur during the initial phases of therapy. [12] Older people often experience multisystem disease and are predisposed to receiving polypharmacotherapy, and they may use warfarin in conjunction with many other drugs. [8]

Warfarin is concomitantly taken with a number of drugs, so it is important to know which medications patients are taking as well. A general practitioner should take this into account since he or she has the most comprehensive understanding of a patient's treatment regimen.

METHODS

The data were collected from outpatients age 45 and above who had received a minimum of 2 prescriptions of systematic medicines over the course of six months, during which the drugs were to be administered at least five days every time. Database included 203,543 patients. Databases did not contain patients prescribed only one drug or one topically applied drug. Also excluded from the study were patients who were treated for less than five days. As soon as the medicine was bought, therapy was considered to have begun, and based on the number of defined daily doses (DDDs) the treatment was considered to have lasted.

The data were further analyzed in separate analyses of patients who were prescribed warfarin therapy (n=7,074). A review of the concomitantly used drugs of patients receiving warfarin therapy was performed for different age groups and genders. In Estonian, the KIS database was used to identify possible drug interactions between the drugs.

A potential interaction between drug pairs is categorized in the database. According to previously published criteria [13], In the KIS database, interactions are categorised according to their risk, outlined in terms of clinical manifestations, and recommended to further action. Depending on the clinical parameters or the drug pair involved, concomitant use may be recommended.

In addition to Epocrates online, two additional databases were used to verify potential interactions: Stockley's Drug Interactions. [12] Physicians frequently use Epocrates online, and according to current literature, it demonstrates a high level of validity. We chose Stockley's handbook as a major source of information on drug interactions because it is the most comprehensive source we are aware of.

Only interactions that appear in all three databases were taken into account. Every patient's treatment regimen was identified in terms of potential interactions. This study only counted one course of a patient's same drug combination if they took it twice in different periods of time.

Polypharmacy is more common in older patients, and this may result in additional interactions that are not warfarin-related and may therefore contribute to adverse reactions. An article found that adverse reactions have increased exponentially occurs as the number of drugs consumed increases linearly. In addition to warfarin, non-warfarin drug interactions were also considered.

SAS software was used to perform the statistical analysis. To compare the means of the two groups, Tukey's test was used to calculate the standard deviation (SD). In addition to linear correlations, Spearman's correlation coefficients were calculated

RESULTS

The total number of patients in the database was 203,543. Patients in the study received 1,935,964 prescriptions over a period of 6 months, of which 655,124 were for systemically active and concomitant drugs. Thirty-four thousand three hundred and thirty-five patients (3.5% of patients) received warfarin therapy, and 34,903 prescriptions were written for them.

Based on the age and gender of patients receiving warfarin treatment, Table 1 shows the distribution of warfarin treatment by gender and age. Drugs used concurrently in the study were: The mean number of drugs taken by women was 4.9 (SD=2.0), compared to 4.7 (SD=2.0) by men (p=0.05). Potential interactions were reported by 1.2 patients on average (SD=1.4). Over the course of a prescribed regimen, women had more potential interactions than men (p = 0.05). (Table1).

Concomitant drugs were normal in the 50¬–60 age group: 4.5 (SD=1.9) when compared to other age group (Table 1). The patients with the fewest concomitant medications (3.6/SD=1.33) (Table 2) were 2,713 (38% of patients treated) with no potential interactions in their treatment regimens. In Table 2, 33% of patients were detected with two or more potential interactions (29%) and 30% were detected with one or more potential interactions (29%) (Table 1). In one patient, there were 13 interactions. Warfarin could cause potential interactions for over half of the patients (57%), and there were 1 to 5 interactions per patient. Five percent of patients receiving warfarin treatment had drug interactions not related to the drug. There is a significant correlation between warfarin interactions and nonsteroidal anti-inflammatory drugs (NSAIDs) (14%), propafenone 5%, amiodarone (7%), amitriptyline 4%, allopurinol 4%. NSAIDs combined with

diuretics and ACE inhibitors were the most common interactions not related to warfarin (5%)

A positive correlation was found between the number of concomitant drugs and the potential interactions (Pearson correlation coefficient 0.985, $p<0.0001$). No other associations were found between gender and age and number of interactions in a multifactorial analysis.

A logistic regression analysis of the 50-60-year-old patient population showed that the odds of encountering a potential interaction between warfarin users were highest among those between 61 and 70 [OR = 1.20; 95% CI 1.06-1.35]. With an OR of 1.21, women were more likely to be exposed than men

Table 1. Age and gender differences in the number of drugs (including warfarin) and potential interactions between warfarin and other drugs.

Age	45-50	50-60	60-65	65+	Total
	N=1283	N=2665	N=2619	N=507	N=7074
All patients No. of drugs (SD)	4.4(1.8) *	4.7(2.2)	4.7(1.0)	4.5(1.7)	4.5(1.7)
No. of potential interactions (SD)	1.2(1.4) *	1.5(1.6)	1.4(1.5)	1.2(1.3)	1.3(1.5)
Men	874	1466	1070	179	3589
No. of drugs (SD)	3.5(1.7)	3.8(2.4)	4.8(1.7)	4.5(1.7)	4.4(2.5)
No. of potential interactions (SD)	1.4(1.5)	1.3(1.6)	1.2(1.7)	1.0(1.4)	1.3(1.5)
Women	510	1206	1427	342	3485
No. of drugs (SD)	4.4(2.2)	4.0(2.2)	4.0(2.)	4.5(1.7)	4.7(2.2)
No. of potential interactions (SD)	1.2(1.4)	1.5(1.2)	1.4(1.3)	1.2(1.3)	1.4(1.5)

Table 2. Mean number of drugs and potential interactions among warfarin users.

No. of potential interactions	**No. of patients**	**No. of drugs Mean (SD)**
0	2714	3.5(1.4)
1	2113	4.8(1.5)
2	1228	5.5(1.6)
3	602	6.5(1.4)
4	285	7.2(1.9)
5	145	7.4(2.2)
6	55	8.2(2.1)
7	21	9.2(2.3)
8	7	9.0(2.4)
9	4	12.4(3.2)
10	3	11.4(1.7)
13	2	13.0(0.0)

DISCUSSION

The study found that 57% of patients with 7,175 potential interactions had interactions with warfarin while 5% of patients had other potential interactions. Increasing prescriptions have led to a rise in potential interactions. It is imperative to avoid drugs that could interact with one another as much as possible because there is a positive correlation between the number of drugs used and the number of possible interactions. An analysis of the literature indicates that potential interactions with warfarin vary widely among patients receiving treatment. The incidence of potential drug interactions has been found to be much higher in some studies. In one study by Verhovsek, *et al*. 79% of 107 long-term care patients receiving warfarin treatments had interacting drugs. A fib was identified as one of the most frequently interacting drugs with warfarin. It was found to interact with acetaminophen, citalopram, acetylsalicylic acid, diltiazem, and simvastatin. It is probably due to the older age group of patients included in that study that potential interactions were more common. During the period of June 1999 to August 2004, Kotirum et al. evaluated the potential interactions between warfarin and patients in Thailand. They found that 83.6% of patients had warfarin-related interactions.

Over-the-counter (OTC) medicines (ibuprofen and aspirin) were included in that study, which may explain the higher percentage of potential interactions. The Estonian government does not require a prescription to purchase aspirin or ibuprofen (400 mg). In our study,

warfarin and NSAIDs are used concomitantly by a large number of patients. The size of the group is therefore likely to be underestimated. As well, in the study by Kotirum *et al*., paracetamol, a drug readily available was the most common interacting drug. The findings of our study showed that warfarin users receive more medications than men: 4.9 (SD=2.0) compared to 4.7 (SD=2.0) and also have a greater number of drug interactions than men. Female gender and polypharmacy in combination with anticoagulant treatment have been linked to increased bleeding risks in previous studies. Ninety-five percent of patients whose treatment regimen contains interacting drugs have an increased risk of bleeding. A study performed by the National Institutes of Health suggests that NSAIDs and warfarin interact profoundly in clinical practice. NSAIDs accounted for 14% of all possible interactions with warfarin in our study (and 24% of all interactions with warfarin in our study). According to Narum *et al*. This drug combination increases bleeding risks by 2–5 times, as compared to warfarin alone. As part of their study of 289 bleeding event cases in Norway, Narum *et al*. discovered that more than half of the patients used drugs that were potentially interfering with warfarin.

NSAIDs co-dispensed with warfarin in only 7.2% cases in a study by Roughead et al. The prevalence of potentially hazardous interactions among Australian veterans was lower than that found in our study. In some studies, a higher percentage of patients were using warfarin and NSAID at the same time. Study findings by Snaith et al. demonstrate that 21% of patients are taking warfarin in combination with NSAIDs. From June 1999 to August 2004, Kotirum et al. examined 1,093 warfarin-treated Thai patients. Their findings showed that 43% of patients taking warfarin also took NSAIDs.

NSAIDs, as well as other drugs, are when used concurrently with warfarin, it increases bleeding risk. In the study, most patients used warfarin concomitantly with simvastatin (9%), amiodarone (7%), propafenone (5%) allopurinol (4%) levothyroxine (4%) and amiodarone (4%). Simvastatin and warfarin interactions may also raise bleeding risks. [12] A few case reports have been published on warfarin and simvastatin interactions. The CYP3A4 enzyme is a substrate of Simvastatin, so its competitive inhibition of the enzyme may interact with warfarin metabolism. In a previous study, it was found that patients who were co-treated with statins had lower plasma 10-hydroxywarfarin concentrations, indicating a slower metabolization of (R)-warfarin. Simvastatin or lovastatin failed to significantly impact the clearance of (R)-warfarin, however, despite its findings. In other studies, simvastatin and warfarin were used simultaneously at levels ranging from 2.6% to 10%. [40] To avoid the mild interaction risk, simvastatin could be replaced by atorvastatin. In our study, the frequency of concomitant use of amiodarone (7%) was also higher than in other studies. There have been numerous studies showing that amiodarone augments warfarin's effects by inhibiting its elimination, especially when concomitant drugs are being used, and this interaction is considered clinically significant.

Hermann et al. reported that 10-hydroxywarfarin concentrations weren't significantly different between patients given warfarin alone or warfarin plus amiodarone under two groups of experimental conditions. Despite the fact that amiodarone interacts with warfarin in a dose-dependent manner, the study by Herman et al. examined patients receiving low doses of the drug.

The warfarin pharmacokinetics of our patients were adversely affected by propafenone (5%), allopurinol (4%), and levothyroxine (4%) coadministration, all of which could result in bleeding. The concentrations of warfarin increased by 38% in healthy volunteers after propafenone was co-administered with warfarin. Therefore, the dose of warfarin should be lowered when it is combined with warfarone. In general, allopurinol does not affect warfarin concentrations in normal clinical dosages. There is little information available on warfarin and levothyroxine interaction. There is some evidence that levothyroxine inhibits warfarin metabolism or decreases its binding to protein. Because of this, this interaction is considered clinically significant.

The results of our study suggest that some patients also took a drug that could reduce the effectiveness of warfarin. During our study, carbamazepine was the only drug that decreased warfarin's effectiveness, and it was only used by 1% of warfarin-using patients. When warfarin and carbamazepine are prescribed together, patients' clearance of the drug is significantly higher. Herman et al. found significant increases in clearance of the (S)- and (R)-warfarin. Furthermore, these patients required more warfarin to achieve desired anticoagulant effects. Kotirum et al. think this interaction could have a significant clinical impact.

Amitriptyline was administered to 4.2% of warfarin-treated patients. This interaction is unclear in terms of clinical significance, but some authors have described INR fluctuations in response to amitriptyline and an anticoagulant co-administered.

The study method we used was prescription-based, so the following questions were not addressed: 1) Following the treatment regimen and taking the prescribed drugs by patients - whether they adhered to it; 2) Drugs that are not prescribed by a physician. In addition to acetaminophen for pain relief, low-dose aspirin for antithrombotic prevention, and other herbal and non-prescription medications, it is not known whether the patients were taking any of those medications as well.; 3)

A diet high in vitamin K-rich foods, alcohol, and tobacco; 4) Clinically manifested adverse reactions and INR values. Patient factors such as age, concomitant diseases, and gender can influence whether potential interactions manifest clinically.

A study of patients' case report forms is being conducted as part of the present research to address the limitations outlined above. Besides the questionnaire, a clinical interaction questionnaire has been developed pertaining to the drugs used in the study. Our preliminary data indicate 15% of those taking warfarin with NSAIDs experience minor bleeding incidents.

CONCLUSIONS

In this study, it was found that 57% of patients in Estonia receiving warfarin also had drugs prescribed that could interact with the drug, and 5% of patients had other interacting drug combinations in their treatment plans. Doctors do not always consider the possibility of interactions when establishing their patients' treatment regimens based on the number of concomitantly used drugs. It is important to note that warfarin interactions are most often associated with increased bleeding risks, particularly when taking NSAIDs (14%), simvastatin (9%), amiodarone (7%), propafenone (5%), allopurinol (4%), and levothyroxine (4%). A total of one drug was found in the regimens included in the study that could reduce the efficacy of warfarin, carbamazepine. There is a high number of outpatients prescribed interacting drugs with warfarin therapy, and most of them result in an increased risk of bleeding. Despite the prevalence of drug interactions in ambulatory care, this study draws attention to the importance of acknowledging them. A careful monitoring of adverse events should be conducted continuously for patients who cannot avoid the use of interacting drugs. General practitioners and pharmacists should also advise patients on warfarin not to use over-the-counter medications.

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