Turkish Journal of Clinics and Laboratory

To cite this article: Uskur T, Guven O, Demireller M. Warfarin in the emergency service: Drug interactions and clinical considerations. Turk J Clin Lab 2024; 2: 234-239

Research Article

Warfarin in the emergency service: Drug interactions and clinical considerations

Acil serviste warfarin: İlaç etkileşimleri ve klinik değerlendirmeler

Tugce Uskur [1]*, Oya Guven [2], Merve Demireller[2]

[1]Kırklareli University, Faculty of Medicine, Department of Medical Pharmacology, Kırklareli, Turkey,
[2]Kırklareli University, Faculty of Medicine, Department of Emergency Medicine, Kırklareli, Turkey.

Abstract

Aim: Drug-drug interactions (DDIs) are common occurrences where one drug influences the blood concentrations or efficacy of another. Warfarin, known for its narrow therapeutic index, carries a heightened risk of severe drug interactions.

Material and Methods: We retrospectively analyzed the records of 211 patients using warfarin at the Emergency Health Services clinic of Kırklareli Training and Research Hospital from January 1, 2020, to December 31, 2020. Patient demographics and drug regimens were documented, and drug interaction assessments were conducted using the drugs.com database.

Results: Among the 211 patients, 17 exhibited signs of bleeding, including 5 with major bleeding and 12 with minor bleeding. Of these, 129 had INR values exceeding 2.5, while 82 had INR values below 2.5. Notably, 11 of the 17 bleeding patients had INR values above 2.5, with an average INR of 3.69. Analysis revealed that the 211 patients collectively used 111 different drugs, with an average of 3.81 drugs per prescription. Intriguingly, 33 of these drugs exhibited major, moderate, or minor inter-actions and were prescribed to 174 patients.

Conclusion: In conclusion, cautious and selective prescription of medications is warranted for patients receiving warfarin due to the potential for significant drug interactions.

Keywords: Warfarin, Drug-Drug Interaction, Emergency Medicine

Corresponding Author*: Tugce Uskur, Faculty of Medicine, Department of Medical Pharmacology
Kırklareli University, Kırklareli, Turkey.
E-mail: tugcebusraerdem@klu.edu.tr
Orchid: 0000-0001-6626-4859
Doi: 10.18663/tjcl.1470923
Recevied: 19.04.2024 accepted: 31.05.2024

Öz

Amaç: İlaç-ilaç etkileşimleri (İİE'ler), bir ilacın diğerinin kan konsantrasyonlarını veya etkinliğini etkilediği yaygın durumlardır. Dar terapötik indeksi ile bilinen warfarin, ciddi ilaç etkileşimleri açısından yüksek risk taşır.

Gereç ve Yöntem: 1 Ocak 2020 ile 31 Aralık 2020 tarihleri arasında Kırklareli Eğitim ve Araştırma Hastanesi Acil Sağlık Hizmetleri kliniğinde warfarin kullanan 211 hastanın kayıtları retrospektif olarak analiz edildi. Hasta demografileri ve ilaç rejimleri belgelendi ve ilaç etkileşim değerlendirmeleri drugs.com veritabanı kullanılarak yapıldı.

Bulgular: 211 hastadan 17'sinde kanama belirtileri görüldü; bunlardan 5'i büyük, 12'si küçük kanamalardı. 129 hastanın INR değerleri 2,5'in üzerindeyken, 82 hastanın INR değerleri 2,5'in altındaydı. Kanama yaşayan 17 hastadan 11'inin INR değeri 2,5'in üzerindeydi ve ortalama INR değeri 3,69'du. Analiz sonucunda, 211 hastanın toplamda 111 farklı ilaç kullandığı ve reçete başına ortalama 3,81 ilaç bulunduğu tespit edildi. İlginç bir şekilde, bu ilaçların 33'ü majör, orta veya minör etkileşimler gösterdiği ve 174 hastaya reçete edildiği görüldü.

Sonuç: Sonuç olarak, warfarin kullanan hastalar için ilaç etkileşimleri potansiyeli nedeniyle ilaç reçetelendirmesi dikkatli ve seçici bir şekilde yapılmalıdır.

Anahtar kelimeler: Varfarin, İlaç-İlaç Etkileşimi, Acil Tıp

Introduction

Emergency departments are vital units providing healthcare services round the clock, offering emergency medical care. There are numerous reasons for emergency department visits (Polat et al., 2005). Adverse drug reactions resulting from drug-drug interactions (DDIs) are also among the reasons for emergency department visits. Drug-drug interaction (DDI) occurs when another drug qualitatively or quantitatively alters the effect of one drug. Drugs' inhibitory or inductive effects on enzymes can increase the toxic effect by reducing the metabolism of other drugs used concomitantly or decrease bioavailability by increasing metabolism (Karabağ, 2019).

DDIs are clinically significant. A literature review conducted in 2004 revealed that DDIs accounted for 0.054% of emergency department visits (Becker et al., 2007). Another study estimated that approximately 2.8% of hospitalizations in the United States were due to DDIs, resulting in more than 245,000 hospitalizations and a healthcare system burden of 1.3 billion dollars annually (Nikolic et al., 2014). It is estimated that DDIs are responsible for approximately 1% of hospital admissions (Bénard-Laribière et al., 2015; Dechanont et al., 2014).

The mechanism where clinically significant drug interactions occur is the inhibition or induction of cytochrome P450 isoenzymes that metabolize drugs (Carpenter et al., 2019). Warfarin, widely used in clinical practice since the beginning of anticoagulant use, is a potent anticoagulant but a drug that requires attention in terms of DDI. Warfarin has different generic names, such as coumadin and orferin. Warfarin is an oral anticoagulant that blocks vitamin K coagulation factors (II, VII, IX, X) and vitamin K-dependent coagulation inhibitors (protein C and S), delaying coagulation. Due to its narrow therapeutic index, susceptibility to drug and food interactions, and difficulties in dose adjustment, warfarin has serious complications such as bleeding (thrombosis, teratogenic effect, necrosis). Bleeding associated with warfarin can be classified as minor bleeding (hematuria, bruising, nosebleeds, and subconjunctival bleeding) and major bleeding (gastrointestinal, pulmonary, intracranial, and retroperitoneal bleeding) (Hall and Wilkins, 2005; Guidelines for warfarin management in the community, 2016).

Additionally, to ensure warfarin's safe and effective use, the drug dose is determined using the International Normalized Ratio (INR) (Wardrop and Keeling, 2008). The INR value is calculated using the formula: INR = (Patient's PT value/Control PT value). PT is the patient's prothrombin time, and ISI is the International Sensitivity Index (Eschenbacher, 2013). High INR values are associated with bleeding, while low INR values are associated with thromboembolism and stroke.

This study will examine the presence and condition of bleeding symptoms, drugs used, and interactions with warfarin in 211 patients using warfarin who presented to the Emergency Health Services clinic of Kırklareli Training and Research Hospital between January 1 and December 31, 2020.

Material and Methods

In this study, data were obtained by retrospectively scanning the files of 211 warfarin-using patients who presented to the Emergency Health Services clinic of Kırklareli Training and Research Hospital between January 1, 2020, and December 31, 2020.

The study was conducted after obtaining approval from the Kırklareli University Ethics Committee.

The date of admission, gender, age, and names of the drugs used were recorded. Drug interaction analyses were performed using the drugs.com database. Drugs used by patients with warfarin in the database were investigated, and a list containing drug interactions was obtained; these interactions were classified as severe, moderate, mild, or no interaction based on their severity.

Data obtained from the study were analyzed using Microsoft Excel. Descriptive statistical methods (frequency (n) and percentage (%)) were calculated when evaluating study data.

Results

When the distribution of 211 patients using warfarin who presented to the emergency department was examined according to gender, it was found that 59.72% were female (126), and 40.28% were male (85) (Figure 1).

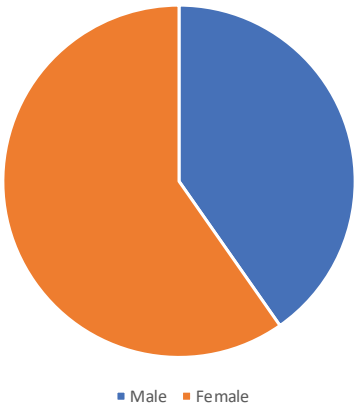

Figure 1. Distribution of patients using warfarin who presented to the emergency department by gender

The mean age of the 211 patients included in the study was 66.9 years; the mean age of the 17 patients with bleeding symptoms was 67.3, and the mean age of the five patients with major bleeding was 78.7. When age groups were examined, one patient each (0.47%) was observed in the 20-29 and 30-39 age groups, 30 patients (14.22%) in the 40-49 age group, 40 patients (18.96%) in the 50-59 age group, 43 patients (20.38%) in the 60-69 age group, 35 patients (16.59%) in the 70-79 age group, 54 patients (25.59%) in the 80-89 age group, and seven patients (3.32%) in the 90-99 age group (Table 1).

Table 1. Distribution of patients using warfarin who presented to the emergency department by age

Age Groups	Number (n)	Percent (%)
20-29 years	1	0,47
30-39 years	1	0,47
40-49 years	30	14,22
50-59 years	40	18,96
60-69 years	43	20,38
70-79 years	35	16,59
80-89 years	54	25,59
90-99 years	7	3,32
Total	211	100

Of the 211 patients, 17 had bleeding symptoms, consisting of 5 with major bleeding and 12 with minor bleeding. INR values of the 211 patients were as follows: 129 had INR values greater than 2.5, and 82 had INR values less than 2.5. Among the 17 patients with bleeding symptoms, 11 had INR values greater than 2.5, 6 had INR values less than 2.5, and the mean INR value of these 17 patients was 3.69.

When the drugs used concomitantly with warfarin by the 211 patients who presented to the emergency department were examined, it was observed that 111 different drugs were used, totaling 804 drugs. The number of drugs listed on prescriptions varied between 1 and 12; an average of 3.81 drugs per prescription were listed.

Metoprolol (44.34%), furosemide (31.22%), amlodipine (19.45%), perindopril (16.28%), digoxin (12.66%), and ramipril (12.66%) were the most commonly prescribed drugs concomitantly with warfarin (Figure 2).

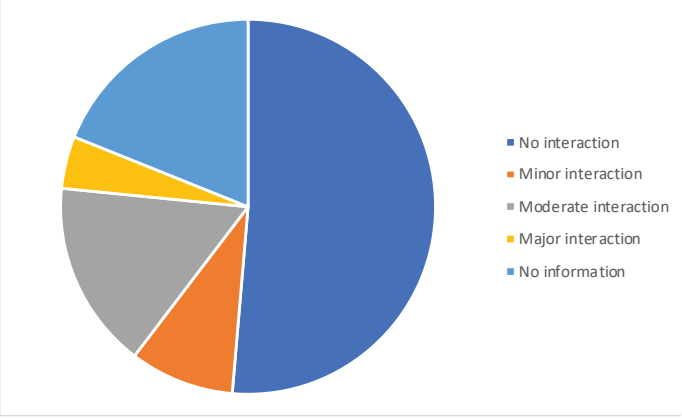

Figure 2. Potential warfarin-drug interactions in prescriptions of patients presenting to the emergency department

According to the analyses performed using the drugs.com database, interactions were found in 34 (33%) of the 111

drugs listed in the prescriptions of the 211 patients; 5 (5%) were severe, 18 (16%) were moderate, and 10 (9%) were minor interactions. While 21 (19%) of the drugs listed on the prescriptions were not in the database, 57 (51%) had no interaction (Figure 2).

Nine of the 211 patients had major interactions with warfarin with amiodarone, aspirin, fenofibrate, carbamazepine, and clopidogrel prescribed (Table 2). Seventy-nine patients with moderate interactions with warfarin were prescribed the following drugs: allopurinol, esomeprazole, escitalopram, fluoxetine, ginkgo, quetiapine, levothyroxine, metformin, methylprednisolone, mirtazapine, nateglinide, pantoprazole, prednisolone, propafenone, rosuvastatin, certolizumab, sertraline, tolterodine. Metformin was included in the prescriptions of 2 patients with major gastrointestinal bleeding, and rosuvastatin and tolterodine were included in the prescriptions of 1 patient with minor gastrointestinal bleeding. Atorvastatin, hydrochlorothiazide, indapamide, methotrexate, pitavastatin, propranolol, cilostazol, spironolactone, tamsulosin, telmisartan, which interacted minorly with warfarin, were included in the prescriptions of 96 of the 211 patients.

Table 2. Frequency of significant drug interactions identified in prescriptions of patients presenting to the emergency department

Drug I	Drug II	N	Frequency Within Serious Interactions (%)	Frequency Within All Prescribed Medications (%)
Warfarin	Fenofibrate	3	33.3	2.7
Warfarin	Carbamazepine	2	22.2	1.8
Warfarin	Clopidogrel	2	22.2	1.8
Warfarin	Amiodarone	1	11.1	0.9
Warfarin	Acetylsalic Acid	1	11.1	0.9
Total		9	100	8.1

Out of the 211 patients using warfarin who presented to the emergency clinic, 12 had minor bleeding, and 5 had major bleeding, totaling 17 patients with bleeding symptoms. All five patients with major bleeding had gastrointestinal bleeding. The first patient with major bleeding had only used piracetam with warfarin, while the other four patients had used multiple drugs. The second patient had used carvedilol, perindopril, and amlodipine with warfarin. The third patient had used metoprolol, ramipril, furosemide, gliclazide, and metformin. The fourth patient had used osteoporosis drugs, SSRIs, asthma drugs, candesartan, amlodipine, and metoprolol, and the fifth patient had used cilostazol, furosemide, carvedilol, valsartan + hydrochlorothiazide, metformin, and insulin concomitantly with warfarin.

Discussion

In this study, a large proportion of patients used different medications together with warfarin, but the rate of drug interactions was low. These were primarily cardiac drugs. The bleeding rate due to warfarin use was low.

Anticoagulant therapy first applied in 1954, is still used to prevent thrombus formation or the growth of thrombin. Warfarin has been one of the most used anticoagulants in clinical settings since its introduction (Moran et al., 2011). The complex dose-response relationship of warfarin affects its safe and effective use. Many drugs can interact with warfarin, enhancing its effects and leading to adverse reactions (Guidelines for Warfarin Management in the Community, 2016). The most significant side effect of warfarin use is bleeding, which can be severe and life-threatening, manifesting as nosebleeds, gastrointestinal bleeding, melena, or bruising (Pirmohamed et al., 2004). Bleeding associated with warfarin accounts for a significant portion of adverse drug reactions requiring hospitalization or occurring in hospitals (Routledge et al., 2004). A study conducted in 2007 showed that warfarin was the most frequently prescribed drug, causing adverse drug reactions and leading to emergency department visits (Budnitz et al., 2007). It has been suggested that warfarin is the most common drug involved in emergency department visits in the United States (Shehab et al., 2016). Therefore, it is essential to investigate emergency department visits related to warfarin and possible drug interactions in this study.

Although the literature reports that the risk of bleeding is high in patients over 60 and 65 years of age using warfarin, the average age of the 17 patients with bleeding symptoms in our study was 67.3, and the average age of the five patients with major bleeding was 71, which is consistent with the literature (Palareti et al., 1996; Wallvik et al., 2007; Campbell and Sefton, 2010).

The INR values of the 211 patients were as follows: 129 had INR values greater than 2.5, and 82 had INR values less than 2.5. Among the 17 patients with bleeding symptoms, 11 had INR values greater than 2.5, 6 had INR values less than 2.5, and the mean INR value of these 17 patients was 3.69. According to the Australian and New Zealand Society of Hematology guidelines for warfarin treatment, the ideal range for INR levels is 2.0-3.0, and when it exceeds 5.0, it becomes clinically unacceptable (Gallus et al., 2000). Therefore, the drug interaction may be more effective than the INR level in the bleeding symptoms of patients using warfarin.

Among the 211 patients using warfarin who presented to the emergency department, the most commonly prescribed drugs concomitantly with warfarin were metoprolol, furosemide, amlodipine, perindopril, digoxin, and ramipril, and these drugs did not interact with warfarin. However, there is no information on drug interactions with warfarin in the drugs.com database for 21 drugs prescribed in 101 of the 211 patients. It is noteworthy that 3 of the five patients with major bleeding used these drugs.

Remarkably, one patient with major bleeding used only piracetam with warfarin, and there is information on their interaction in the drugs.com database. It is stated in the literature that piracetam may decrease the clearance rate of Warfarin, leading to higher serum levels (https://go.drugbank.com/drugs/DB09210). Considering that this patient was an 86-year-old male, it is highly probable that the clearance rate of warfarin was slowed down. A study investigating the risk and severity of bleeding complications in elderly patients treated with warfarin suggests that warfarin can cause life-threatening and fatal complications, especially in patients aged 80 and over (Fihn et al., 1996). Therefore, caution should be exercised in elderly patients regarding warfarin and drugs prescribed concomitantly with warfarin.

The second patient with major bleeding used carvedilol, perindopril, and amlodipine with warfarin. Although these three drugs do not directly interact with warfarin, amlodipine has a moderate interaction with carvedilol (Henry et al., 1985) and a minor interaction with perindopril (Kaplan, 1991).

The third patient with major bleeding used metoprolol, ramipril, furosemide, gliclazide, and metformin with warfarin. While metoprolol, ramipril, and furosemide do not interact with warfarin, there is no information about the interaction of gliclazide with warfarin. Metformin has a moderate interaction with warfarin, and this interaction is indicated as a risk of hypoglycemia in the database (www.drugs.com).

The fourth patient with major bleeding who presented to the emergency department used osteoporosis drugs, SSRIs, asthma drugs, candesartan, amlodipine, and metoprolol with warfarin. There is a moderate interaction between metoprolol and amlodipine that may cause adverse cardiovascular effects. Additionally, some SSRIs (Fluoxetine and Fluvoxamine) inhibit CYP2C9, the enzyme that metabolizes warfarin. Therefore, they increase the risk of bleeding.

The last patient with major bleeding who presented to the emergency department used cilostazol, furosemide, carvedilol, valsartan + hydrochlorothiazide, metformin, and insulin concomitantly with warfarin. There is a clinically insignificant minor interaction between cilostazol and hydrochlorothiazide with warfarin in this patient. As age increases, the likelihood of multiple diseases and, consequently, the number of drugs used increases, increasing the risk of bleeding in individuals.

In addition to the drugs used concomitantly with warfarin in these 17 patients with bleeding symptoms, many demographic and clinical factors, such as age, gender, health status, genetic differences, nutrition, timing of drug intake, and interindividual variability in dose requirements, may also be effective.

Conclusion

In conclusion, 804 medications belonging to 111 different types were prescribed, along with warfarin among 211 patients. Notably, 33 of these medications had varying degrees of major, moderate, or minor interactions and were prescribed to 174 patients. In summary, it is essential to remember that warfarin drug interactions can lead to severe consequences, emphasizing the importance of raising awareness among prescribing physicians and patients receiving treatment to be cautious in this regard.

Conflict Of Interest

All authors declared no competing interests in this work.

Ethics Committee Approval

The study was conducted after obtaining approval from the Kırklareli University Ethics Committee (P202400011/01-03.04.2024).

Financial Support

This study received no financial support.

Conflict of Interest

The authors declare no conflict of interest.

References

1. Becker M, Kallewaard M, Caspers PWJ, Visser LE, Leuens HGM and Stricker BH Ch, Hospitalisations and emergency department visits due to drug-drug interactions: a literature review, Pharmacoepidemiol. Drug Saf. 2007; 16(6) :641–51.
2. Bénard-Laribière A, Miremont-Salamé G, Pérault-Pochat M-C, Noize P, Haramburu F. The EMIR study group on behalf of the French network of pharmacovigilance centres. Incidence of hospital admissions due to adverse drug reactions in France: the EMIR study. Fundam Clin Pharmacol. 2015;29(1):106-11.
3. Budnitz DS, Shehab N, Kegler SR, Richards CL. Medication use leading to emergency department visits for adverse drug events in older adults. Ann Intern Med. 2007;147(11):755–65.

4. Campbell CJ, Sefton M. Discharge teaching about warfarin: patient retention of knowledge. Have home care patients been taught what they need to know. Home Healthcare Nurse. 2010;28(6):366-74.
5. Carpenter M, Berry H, Pelletier AL. Clinically Relevant Drug-Drug Interactions in Primary Care. Am Fam Physician. 2019;99(9):558-64.
6. Dechanont S, Maphanta S, Butthum B, Kongkaew C. Hospital admissions/visits associated with drug–drug interactions: a systematic review and meta-analysis. Pharmacoepidemiol Drug Saf. 2014;23(5):489-97.
7. Eschenbacher L. PT, INR, and APTT testing. Washington State Department Of Health Elaborations News And İssues For Washington's Clinical Laboratories. 2018;23(2):1-5.
8. Fihn SD, Callahan CM, Martin DC, McDonell MB, Henikoff JG, White RH. The risk for and severity of bleeding complications in elderly patients treated with warfarin. The National Consortium of Anticoagulation Clinics. Ann Intern Med. 1996;124(11):970-9.
9. Gallus AS, Baker RI, Chong BH, Ockelford PA, Street AM. Consensus guidelines for warfarin therapy. Recommendations from the Australasian Society of Thrombosis and Haemostasis. Med J Aust. 2000;172(12):600-5.
10. Guidelines for warfarin management in the community, January. 2016
11. Hall AM, Wilkins MR. Warfarin: a case history in pharmacogenetics, Heart 2005;91(5):563-564.
12. Henry M, Kay MM, Viccellio P. Cardiogenic shock associated with calcium-channel and beta blockers: reversal with intravenous calcium chloride. Am J Emerg Med. 1985;3(4):334-6.
13. Kaplan NM. Amlodipine in the treatment of hypertension. Postgrad Med J. 1991;67 Suppl 5:s15-9.
14. Karabağ E. Concurrent Use of NSAIDs in Patients Taking Metoprolol and Drug Interaction. [Master's dissertation]. Istanbul Medipol University. Istanbul. 2019.
15. Moran SM, Fitzgerald N, Pope M, Madden M, Vaughan CJ. Warfarin anticoagulation: a survey of patients' knowledge of their treatment. Ireland Journal Medicine Science. 2011; (180):819-22.
16. Nikolic B, Jankovic S, Stojanov O, Popovic J. Prevalence and predictors of potential drug-drug interactions. Cent Eur J Med. 2014;9(2):348-56.
17. Palareti G, Leali N, Coccheri S, Poggi M, Manotti C, D'Angelo A, Pengo V, Erba N, Moia M, Ciavarella N, Devoto G, Berrettini M, Musolesi S. Bleeding complications of oral anticoagulant treatment: an inception-cohort, prospective collaborative study (ISCOAT). Italian Study on Complications of Oral Anticoagulant Therapy. Lancet. 1996;348(9025):423-8.
18. Pirmohamed M, James S, Meakin S, Green C, Scott AK, Walley TJ, et al. Adverse drug reactions as cause of admission to hospital: Prospective analysis of 18 820 patients. BMJ. 2004;329(7456):15–9.
19. Polat O, Kabaçam G, Güler İ, Ergişi K, Yıldız A. Surveillance analysis of patients presenting to the Ibn-i Sina Hospital Emergency Department. Turk J Emerg Med. 2005;5(2):78-81.
20. Routledge PA, O'Mahony MS, Woodhouse KW. Adverse drug reactions in elderly patients. Br J Clin Pharmacol. 2004;57(2):121–6.
21. Shehab N, Lovegrove MC, Geller AI, Rose KO, Weidle NJ, Budnitz DS. US Emergency Department visits for outpatient adverse drug events, 2013-2014. JAMA. 2016;316(20):2115–25.
22. Wallvik J. Sjalander A. Johansson L. Bjuhr O. Jansson JH. Bleeding complications during warfarin treatment in primary healthcare centres compared with anticoagulation clinics. Scand J Prim Health Care. 2007; 25(2): 123-28.