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Original Article

Potential Drug-Drug Interactions in Patients Using Warfarin, Heparin, and Enoxaparin

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Abstract

Background: Drug-drug interactions can often lead to preventable adverse drug events and hospitalization. However, the clinical outcome of a potential drug-drug interaction that may range from minor alterations to major toxicity or loss of effect is often unknown. Drugs with narrow therapeutic index are more susceptible to the outcomes of interactions. Anticoagulants are one of the drug groups prone to drug-drug interactions and have important side effects. in this retrospective study, the frequency of drug-drug interactions involving warfarin, heparin and enoxaparin was investigated.

Methods: Overall, 300 patients (including 55% males with an average age of 50.75 years) participated in this study, and for each anticoagulant, 100 patient orders were randomly selected from the hospital system. Drug-drug interactions were evaluated using the Micromedex drug interaction checker.

Results: A total of 1691 drug-drug interactions (306 major, 253 moderate, and 89 minor interactions) were recorded of which only 648 (average 2.16) involved warfarin, heparin, or enoxaparin. Most interactions were recorded in patients admitted to the cardiovascular surgery (n=312) and cardiology (n=119) wards. There was a significant relationship between the number of drugs and the frequency of interaction. warfarin had the highest number of interactions (n=388).

Conclusion: The frequency of drug interactions is high in patients on anticoagulant therapy. The efficacy and safety of these drugs can be affected by drug interactions. Accordingly, these interactions should always be considered, especially in patients with multiple drug use. Efficient monitoring strategies should be employed to optimize treatment while reducing adverse effects.

Keywords: Drug-drug interactions, Warfarin, Enoxaparin, Heparin

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Introduction

Drug-drug interactions can mostly result in preventable adverse drug events. The clinical outcomes of a potential drug-drug interaction are often unknown, and epidemiological data are rare. The consequences of drug-drug interactions range from minor alterations to major toxicity or loss of effect. According to published studies, these interactions account for 1% of all hospitalizations and 16% of all patients hospitalized for adverse drug reactions (1-3). Based on evidence from a study conducted in the internal medicine service, 56.2% of patients were exposed to one or more major or intermediate potential drug-drug interactions (4). The use of multiple drugs for the treatment of diseases is quite common, especially in the elderly and other patients with multiple comorbidities. The incidence of drug interactions is associated with the type of the applied drugs and the number of concurrently used drugs. Polypharmacy, which is defined as the routine use of five or more drugs, is a major factor that increases the likelihood of adverse drug reactions and drug-drug interactions, thus making therapeutic goals difficult to achieve (5-10). Not all drug-drug interactions are clinically significant. Most interactions go unnoticed because of the absence of new clinical symptoms, and some interactions are often indicated to worsen the already existing symptoms. A lack of knowledge, low motivation, and poor attitudes are attributed to the lack of documentation of interactions (6-10).

Anticoagulants are used for various indications. Warfarin can be applied for the prophylaxis and treatment

of thrombotic and embolic events; it reduces the risk of death, recurrent myocardial infarction, and stroke or systemic embolism after myocardial infarction. Parenteral anticoagulants heparin and enoxaparin also have similar indications (11).

Anticoagulant drugs are susceptible to various drug-drug interactions. These interactions are usually clinically significant as these drugs have narrow therapeutic windows (warfarin), need monitoring, and have serious side effects (12).

The aim of the study was to determine the frequency of potential drug-drug interactions in hospitalized patients treated with warfarin, heparin, and enoxaparin using the Micromedex online drug interaction checker.

Materials and Methods

This retrospective study was conducted at a university-affiliated teaching hospital. Adult patients receiving either warfarin, heparin, or enoxaparin were searched in the hospital system. A total of 300 different patients were included in the study. Each drug was searched in the hospital's online record system, and 100 patients' orders containing each drug and at least one other drug were selected at random. Patients' information, including age, ward, and medication orders, was obtained from the hospital data system. For each patient, one medication order containing at least one of the anticoagulants was assessed for drug interactions using the Micromedex drug interaction checker. Interactions were evaluated as contraindicated, major, moderate, and minor. The distribution of interactions was evaluated based on the total number of drugs in the order and the type of the anticoagulant. The number of drugs on the patients' orders was also assessed in terms of polypharmacy. Orders were categorized into normal (<5 drugs), polypharmacy (6-9 drugs), and hyperpolypharmacy (≥10 drugs) groups based on the number of drugs (5). The association between the number of drugs and the frequency of interactions was examined as well.

Statistical Analysis

All data were analyzed using SPSS (Statistical Package for Social Sciences), version 25.0. Continuous variables are expressed as the mean ± standard deviation; ordinal and nominal data are expressed as number (%). The Spearman's rank correlation test was used to analyze the correlation between interactions and patient groups based on the number of drugs in their orders (normal, polypharmacy, and hyperpolypharmacy). A P value <0.05 within a confidence interval of 95% was considered statistically significant.

Ethics Committee Approval

The study was approved by the Istanbul Medipol University Non-Interventional Clinical Research Ethics Committee by decision number 10840098-604.01.01-E.1687.

Results

Adult patients who received warfarin, heparin, and/or enoxaparin were randomly selected from the hospital system. Demographic data and medication orders of 300 patients were recorded. Overall, 55% (167) of the patients were males with a mean age of 50.75±25.57. The mean age of female patients was 54.20±25.80. The selected patients were admitted to 25 different departments in the hospital; most of the patients were admitted to the cardiovascular surgery ward.

The average number of drugs used by the patients was 1.5 with a total of 440 drugs. One patient's order contained 33 drugs, which is the maximum number of drugs used in the study population. Seven patients' orders contained only two drugs. The majority (93.67%) of the patients were using more than five drugs. Based on the number of drugs in the patients' orders, 19, 123, and 158 patients were in the normal, polypharmacy, and hyperpolypharmacy groups, respectively.

Patients' orders were individually assessed for drug interactions using the Micromedex drug interaction checker. A total of 1691 drug interactions were identified with an average of 5.64 interactions per patient. The frequency of interactions increased with the number of drugs (P<0.001). There were 18 contraindicated, 818 major, 766 moderate, and 89 minor interactions. Each type of drug interaction was correlated with the groups based on the number of medications (Table 1).

The distribution of identified interactions based on hospital departments was evaluated, and most contraindications were recorded in patients admitted to the cardiology ward. More interactions were recorded in patients admitted to the cardiovascular surgery ward with an average of 10.68 interactions per patient; more precisely, 598 drug interactions were recorded in 56 patients in this ward. Two of these interactions were contraindicated 273, 283, and 40 of them were major, moderate, and minor interactions, respectively. Data on the distribution of

Table 1. Correlation Between Number of Drugs and Interactions

Medication Order Groups (Number of patients)	Total Interactions	Contraindicated Interactions	Major Interactions	Moderate Interactions	Minor Interactions
Normal (n=19)	40	0	20	18	2
Polypharmacy (n=123)	206	1	94	103	8
Hyperpolypharmacy (n=158)	1445	17	704	645	79
Total (n=300)	1691	18	818	766	89
P value	< 0.001	< 0.006	< 0.001	< 0.001	< 0.001

Table 2. Distribution of Total Drug Interactions Among Wards and Their Severity

Ward	No. of Patient	Severity of Interaction				Total	Average Interaction
		Contraindicated	Major	Moderate	Minor		
Anesthesia and Reanimation	41	1	77	81	18	177	4.317
Brain and Nerve Surgery	1	0	1	2	0	3	3
Cardiology	43	7	162	173	14	356	8.279
Cardiovascular Surgery	56	2	273	283	40	598	10.678
Chest Diseases	2	0	1	2	1	4	2
Gastroenterology	1	0	2	5	0	7	7
General Surgery	14	0	26	5	0	31	2.214
Gynecology and Obstetrics	3	0	8	2	0	10	3.333
Hematology	12	4	41	15	1	61	5.083
Infectious Diseases and Clinical Microbiology	2	0	0	0	0	0	0
Internal Disease	15	0	39	33	0	72	4.8
Medical Oncology	14	2	36	18	0	56	4
Nephrology	3	0	2	3	0	5	1.667
Neurology	14	0	10	29	1	40	2.857
Newborn	23	0	25	19	10	54	2.347
Organ Transplantation	12	0	18	8	0	26	2.167
Orthopedics and Traumatology	12	0	20	33	0	53	4.417
Pediatric Cardiology	3	0	3	3	0	6	2
Pediatric Chest Diseases	1	0	0	0	0	0	0
Pediatric Hematology and Oncology	8	1	8	10	2	21	2.625
Pediatry	9	1	43	25	1	70	7.778
Physical Medicine and Rehabilitation	3	0	9	8	0	17	5.667
Radiology	1	0	3	0	0	3	3
Thoracic Surgery	6	0	11	9	1	21	3,5
Urology	1	0	0	0	0	0	0
Total	300	18	818	766	89	1691	5.64

interactions are provided in Table 2.

Out of the total 1691 recorded drug interactions, only 648 involved the anticoagulants of interest. Overall, 306, 253, and 89 major, moderate, and minor interactions were recorded, respectively. There were no contraindicated interactions. Based on the results, 388, 114, and 148 interactions were recorded for warfarin, heparin, and enoxaparin, respectively. Of the total 648 interactions, 312, 119, 51, and 40 were recorded in the cardiovascular surgery, cardiology, anesthesia and reanimation, and internal medicine wards, respectively. In drug orders from the cardiovascular surgery department, 68 major and 135 moderate, as well as 46 major and 25 moderate interactions were recorded for warfarin and heparin, respectively. In addition, 37 major interactions and 1 moderate interaction were recorded for enoxaparin. Table 3 provides the distribution of these interactions based on wards. Enoxaparin and warfarin combination was used in 42 patients, representing the highest number of major interactions. Warfarin-tramadol interaction was the most (n=33) recorded moderate interaction. The frequencies of major and moderate interactions are presented in Tables 4 and 5, respectively.

Discussion

Drug-drug interactions are frequent and considered a major concern for both clinicians and patients. The risk of interactions increases with increase in the number of concurrently used drugs. Polypharmacy is an independent factor that increases the risk of interactions and contributes to adverse drug reactions and treatment complications (5). Based on the findings, a higher number of interactions was recorded in medication orders containing more than ten medications. Multiple uses of drugs are unavoidable in some situations, especially in patients with comorbidities.

Anticoagulants have been associated with high incidences of drug interactions. In this study, most interactions were recorded for warfarin, while heparin had the least number of interactions. In a prospective study conducted on 133 patients using warfarin, 428 warfarin-related drug interactions were recorded (13). In the current study, a similar number of warfarin-related interactions was recorded in the warfarin group. Drug interactions resulting in changes in the efficacy of warfarin can be tracked with changes in the international normalized ratio (INR) values. Mcdonald et al reviewed the rate of warfarin

Table 3. Distribution and Severity of Drug Interactions Involving Anticoagulants

Ward	Warfarin		Heparin		Enoxaparin		Total
	Major	Moderate	Major	Moderate	Major	Moderate	
Anesthesia and Reanimation	9	15	5	1	12	0	51
Brain and Nerve Surgery	1	2	0	0	0	0	3
Cardiology	24	49	8	2	22	0	119
Cardiovascular Surgery	48	131	38	6	37	1	312
Gastroenterology	1	4	0	0	0	0	5
General Surgery	0	0	1	0	7	0	8
Gynecology and Obstetrics	1	1	0	0	3	0	5
Hematology	3	0	4	0	5	0	15
Internal Medicine	14	12	1	0	9	0	40
Medical Oncology	0	0	1	1	7	1	11
Nephrology	1	1	1	0	2	0	5
Neurology	4	15	1	0	3	0	26
Newborn	0	0	2	0	0	0	9
Organ Transplantation	2	3	2	0	5	0	15
Orthopedics and Traumatology	1	5	0	0	8	0	14
Paediatric Cardiology	1	2	1	0	2	0	7
Pediatric Hematology and Oncology	0	0	0	0	0	0	2
Pediatry	0	0	1	0	0	0	2
Physical Medicine and Rehabilitation	1	1	0	0	3	0	7
Radiology	0	0	1	0	0	0	2
Thoracic Surgery	0	0	0	0	3	0	3
Total	111	241	67	10	128	2	661

interactions in 3129 patients and recorded abnormal INR values in 230 patients with warfarin-amiodarone interactions (14). We also recorded a good number of warfarin-amiodarone interactions (n=18), but we did not review the INR values of our patients as it was not part of our objective.

Khurram et al evaluated the risk of bleeding associated with the use of warfarin in 107 postoperative patients receiving dual antiplatelet therapy (aspirin + clopidogrel). They revealed a significant increase in the risk of major and minor bleeding associated with warfarin use (15). Warfarin, aspirin, and clopidogrel are the most commonly used drugs in patients with heart diseases. In our study, warfarin was frequently and occasionally used with aspirin and clopidogrel, respectively. It should be noted that the risk of bleeding will increase with concurrent use.

In a case report, Recker and Kier found an increase in the warfarin effect with an acute elevation in the INR from 2.1 to 16.8 after a 14-day clarithromycin regimen (16), highlighting the extent and importance of antibiotic-altered vitamin K synthesis. We recorded seven warfarin-clarithromycin interactions. A close follow-up is required when antibiotics known to affect vitamin K production are prescribed to patients using warfarin.

The concurrent use of two or more anticoagulants increases the risk of bleeding, but concurrent use is reported in some situations. Heparin and enoxaparin are usually used for bridging anticoagulation when warfarin therapy is initiated until is achieved the INR target (17,18). The administration of low-molecular-weight heparin for 5-10 days, as a bridging anticoagulation therapy with warfarin, in the treatment of deep vein thromboembolism is reported to be safe and efficient in comparison to conventional anticoagulation (19,20). We recorded the use of these combinations in 71 patients, the majority of whom were admitted to the cardiovascular surgery ward. These combinations are typically prescribed for patients with cardiovascular interventions, which is in line with our results. We assume that these combinations were appropriately administered in line with the guidelines. Nevertheless, it can be mentioned that the clinical and laboratory monitoring of symptoms is necessary when concurrent use is unavoidable and/or indicated .

In our study, warfarin had the highest number of interactions (60.5%). Heparin and enoxaparin are not orally used anticoagulants; therefore, they cannot be desired alternatives to warfarin. Parenteral administration of heparin and enoxaparin affects patients' compliance with treatment. The direct thrombin inhibitor (i.e., dabigatran) and direct factor Xa inhibitors (i.e., apixaban, betrixaban, edoxaban, and rivaroxaban) are newer oral anticoagulants with fewer drug-drug interaction potentials. These drugs can be better alternatives for patients who are at risk of drug interactions (11,17).

Table 4. List and Frequency of Recorded Major Interactions

Interacting drug	Enoxaparin	Heparin	Warfarin
Alprostadil		2	
Alteplase	1		
Alteplase		1	
Amiodarone HCl			18
Amoxicillin/clavulanic acid			1
Ampicillin/sulbactam sodium			1
Aspirin		22	24
Bemiparin sodium	1	1	1
Carbidopa/entacapone/levodopa			1
Ceftazidime			2
Ciprofloxacin			1
Citalopram	2	1	
Clarithromycin			7
Clopidogrel	12	5	4
Diclofenac	15	3	2
Dipyrone (Metamizole)			17
Escitalopram	2	4	3
Fluoxetine		1	
Heparin	26		0
Ketoprofen	4	1	
Levofloxacin			2
Linezolid			1
Metamizole	8	17	
Metronidazole			3
Miconazole			1
Moxifloxacin			3
Nepafenac	1	1	
Orlistat		2	
Oseltamivir Phosphate			2
Paroxetine HCl			1
Penicillin G Potassium			1
Piperacillin/tazobaktam sodium			6
Piracetam	3	3	3
Piroxicam		1	
Prasugrel	2		
Sertraline	1	2	2
Tenoxicam	8		2
Valproic acid			1
Venlafaxine			1
Warfarin	42		
Total	128	67	111

Table 5. Frequency of Recorded Moderate Interactions

Interacting Drug	Enoxaparin	Heparin	Warfarin
Duloxetine HCl	1	1	
Vitamin A		1	
Perindopril		1	
Captopril		1	
Ascorbic acid/folic acid		6	
Calcium gluconate	1		
Ceftriaxone sodium			15
Acetaminophen (Paracetamol)			23
Lactulose			6
Pantoprazole sodium			24
Cefazoline sodium			30
Ranitidine HCl			31
Tramadol HCl			33
Esomeprazole magnesium			12
Hydrochlorothiazide/ spironolactone			12
Cefoperazone sodium			1
Levothyroxine sodium			6
Lansoprazole			3
Dexamethasone			3
Quetiapine fumarate			1
Rosuvastatin calcium			2
Tigecycline			1
Vancomycin HCl			1
Glimepiride			1
Propafenone HCl			2
Rifampin			1
Propranolol			1
Prednisolone			2
Ezetimibe			1
Heparin			29
Total	2	10	241

Conclusion

In this study, we recorded relatively important drug interactions involving the most frequently used anticoagulants. These interactions involve other medications commonly used in patients with indications that necessitate anticoagulant use. These interactions can affect the efficacy and safety of these drugs. To optimize therapy drug interactions should always be considered in patients receiving anticoagulant therapy, especially patients with multiple comorbidities. Eventually, efficient monitoring strategies should be employed to optimize treatment while reducing adverse effects.

Conflict of Interests

The authors report no conflict of interests.

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