Original Work

Assessment of Potential Drug Interactions That May Increase the Risk of Major Bleeding Events in Patients on Warfarin Maintenance Therapy

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Abstract

Objectives: To assess whether drug interactions were present in patients on warfarin maintenance therapy who experienced a major bleeding event and assess which medications may increase the incidence of major bleeds. This information will be used to enhance prescription and monitoring protocols within the Marshfield Clinic Anticoagulation Service (ACS).

Methods: A retrospective electronic record review of patients enrolled in the ACS on maintenance warfarin therapy between March 1, 2011 and September 30, 2014 was conducted to analyze adverse bleeding events. Cases were patients on warfarin therapy who experienced major bleeding events. Date of major bleeding event was used as a reference date to evaluate interaction potential of medications taken 30 days before the major bleeding event.

Results: From a total of 115 drugs analyzed, 34 were significantly associated with major bleeding events with concurrent warfarin treatment ($p < 0.05$); 17 medications had previously documented warfarin drug interaction in Micromedex®. Analyses of medications initiated within 14 days before major bleeding event reference date identified furosemide, hydrocodone-acetaminophen, amoxicillin-clavulanate, acetaminophen, docusate, and metoprolol tartrate as significantly associated with major bleeding events ($p < 0.05$).

Conclusions: Even when closely managed by an anticoagulation service, patients can experience major bleeding events due to potentially unknown/unrecognized drug interactions with warfarin. Further analysis of individual drug interactions with warfarin will determine if current protocols regarding warfarin medication management should be altered in relation to various drugs.

Warfarin is an anticoagulant that inhibits vitamin K epoxide reductase to prevent the synthesis of coagulation factors.[1,2] Warfarin is highly bound to plasma proteins and has a half-life of 36 to 42 hours.[3] Multiple cytochrome P450 (CYP) enzymes including CYP2C9, 2C19, 2C8, 2C18, 1A2, and 3A4 metabolize warfarin in the liver.[1] Warfarin is a racemic mixture of R and S enantiomers, of which the S enantiomer is approximately three times more potent in terms of anticoagulant properties than the R enantiomer.[3] The S enantiomer is primarily metabolized by the CYP2C9 enzyme and to a lesser extent CYP3A4, while the R enantiomer is primarily metabolized by CYP1A2 and CYP3A4 and to a lesser extent by CYP2C19.[3] Medications that increase bleeding on their own can cause pharmacodynamic interactions with warfarin. In addition to drug interactions, pharmacogenetics, variation in a patient's diet and drug-disease interactions can also increase risk of major bleeding events.[1] Warfarin has multiple documented pharmacokinetic and pharmacodynamic drug interactions that lead to increased bleeding risk.[1,3]

Medications that inhibit or induce CYP2C9, CYP1A2, and CYP3A4 can potentially cause drug interactions with warfarin.[1] Inhibitors of one or more of these CYP enzymes increase patient risk for bleeding during warfarin treatment, while inducers of one or more of these enzymes increase patient risk for thromboembolism with concurrent warfarin treatment. Previous studies have demonstrated the importance of monitoring potential drug interactions with respect to risk management during warfarin therapy.[4,5] However, it is unclear how much impact these potential interactions have with respect to bleeding risk in a well-managed patient population, where healthcare providers are actively monitoring for such interactions. The Marshfield Clinic Anticoagulation Service (ACS) manages approximately 10,000 to 11,000 patients on warfarin per 12 month period with a protocol driven service. Micromedex® is the drug database used most frequently to identify potential drug interactions.

The goal of this study was to evaluate a population of patients enrolled in the Marshfield Clinic Anticoagulation Service (ACS) who experienced a major bleeding event while on warfarin and to assess the risk of an adverse bleeding event in the presence of drug interactions with warfarin.

Methods

This retrospective study was approved by the Marshfield Clinic Institutional Review Board. The study included patients over the age of 18 years enrolled in the Marshfield Clinic ACS on maintenance warfarin therapy between March 1, 2011 and September 30, 2014. Maintenance therapy was defined as more than 30 days of warfarin therapy, and case subjects were those patients who experienced major bleeding events while taking warfarin. For this study, major bleeding events were defined as bleeding events resulting in hospitalization, blood transfusion, or death. The date of the major bleeding event was used as the reference date for evaluating the interaction potential of medications taken within 30 days prior to the major bleeding event.

A frequency-matched group of control subjects was randomly selected from the same ACS population. Matching criteria included gender, age, and duration of warfarin therapy; the matching groups included five age categories (18–54 years, 55–64 years, 65–74 years, 75–84 years, and ≥85 years), two gender categories (male and female), and four categories for year of initial exposure to warfarin (before 2002, 2003–2007, 2008–2011, 2012–2014). In addition, a counterfactual event date was assigned to each control subject by randomly sampling (with replacement) the actual event dates of matched case subjects who experienced their major bleeding event at a time when both case and control patients were managed by the ACS. This method of assigning reference event dates was used to ensure comparable distributions of dates for the two groups. Patients who were bridged on enoxaparin within 2 weeks before the reference date were ineligible for either group.

A list of newly prescribed medications within 2 weeks from the reference date was retrieved from the electronic health record (EHR) for all study subjects. The start date for each newly prescribed medication was identified to verify the patient had not previously been on the medication. To determine which drugs could have contributed to the major bleeding event, all medications recorded in each patient's medication list within 30 days of the major bleeding event reference date were also abstracted from the EHR. The last International Normalized Ratio (INR) before the reference date was abstracted electronically for both case and control patient groups. The electronic data (including information for all bleeding events during the 30-day time period preceding the major bleeding event) were validated by manual review. In addition, patients were randomly selected for manual review of their eligibility and medication information. The criteria for the electronic retrievals were iteratively adjusted based on the manual review. Full manual review was performed for 70 case and 70 control subjects included in the final analysis. Potential warfarin drug interactions while taking oral medications was the primary focus this study. Of the generic name medications found during manual chart review, 85% were found both electronically and manually which was deemed acceptable. Other routes of administration for medications, such as transdermal, ophthalmic, or inhaled were not analyzed or included when assessing the total number of drugs the patient was taking 30 days prior to the reference date. Prescriptions for enoxaparin and phytonadione were not included in the final analysis of drug interactions with warfarin due to the use of these medications as a part of warfarin anticoagulation management. For example, if phytonadione was included in the study, it would have likely shown up in the analysis as a potential drug interaction, when in fact it is used as a reversal agent to warfarin. However, the patients that took phytonadione were included in the study.

The primary statistical analyses were based on multiple logistic regression models with the case/control indicator as a binary response. These models included the matching criteria and the exact age as covariates with a drug indicator as the predictor of primary interest. To prevent convergence problems and to limit spurious

TABLE 1. Drugs on Medication List in Order of Descending Odds Ratio

Generic Drug Name	*No. of Case Group Patients on Drug (%)*	*No. of Control Group Patients on Drug (%)*	*Odds Ratio (95% Confidence Interval)*	*P-value*
A. 30 days prior to the reference date				
Oxycodone	62 (8.1)	15 (2)	4.5 (2.6-8.2)	<0.001
Prochlorperazine	37 (4.8)	12 (1.6)	3.4 (1.8-6.8)	<0.001
Levofloxacin*	41 (5.3)	13 (1.7)	3.3 (1.8-6.6)	<0.001
Dextromethorphan-guaifenesin	23 (3.0)	7 (0.9)	3.3 (1.5-8.3)	0.007
Clopidogrel*	16 (2.1)	5 (0.7)	3.3 (1.3-10.1)	0.022
Oxybutynin chloride	36 (4.7)	12 (1.6)	3.1 (1.7-6.3)	<0.001
Pregabalin	15 (2.0)	5 (0.7)	3.1 (1.2-9.7)	0.029
Gemfibrozil*	26 (3.4)	9 (1.2)	3.0 (1.4-6.7)	0.006
Baclofen	15 (2.0)	6 (0.8)	2.8 (1.1-8.1)	0.037
Calcitriol	17 (2.2)	6 (0.8)	2.8 (1.2-7.9)	0.031
Metolazone	32 (4.2)	12 (1.6)	2.7 (1.4-5.6)	0.003
Amoxicillin-clavulanate*	30 (3.9)	12 (1.6)	2.6 (1.4-5.4)	0.005
Ferrous sulfate	120 (16)	53 (6.9)	2.5 (1.8-3.6)	<0.001
Ibuprofen*	17 (2.2)	7 (0.9)	2.4 (1.1-6.4)	0.049
Diphenhydramine-acetaminophen*	25 (3.3)	12 (1.6)	2.2 (1.1-4.5)	0.029
Hydrocodone-acetaminophen*	167 (22)	88 (11)	2.2 (1.6-2.9)	<0.001
Cephalexin*	30 (3.9)	14 (1.8)	2.2 (1.2-4.3)	0.018
Ondansetron	40 (5.2)	20 (2.6)	2.1 (1.2-3.7)	0.010
Glimepiride*	34 (4.4)	17 (2.2)	2.0 (1.1-3.8)	0.019
Paroxetine*	28 (3.6)	14 (1.8)	2.0 (1.1-4.0)	0.034
Amoxicillin*	73 (9.5)	41 (5.3)	1.9 (1.3-2.9)	0.001
Amiodarone*	38 (4.9)	20 (2.6)	1.9 (1.1-3.4)	0.021
Loperamide	42 (5.5)	23 (3.0)	1.9 (1.1-3.2)	0.019
Acetaminophen*	373 (49)	267 (35)	1.8 (1.5-2.3)	<0.001
Citalopram*	66 (8.6)	39 (5.1)	1.8 (1.2-2.7)	0.006
Polyethylene glycol 3350	57 (7.4)	34 (4.4)	1.7 (1.1-2.7)	0.017
Furosemide	397 (52)	299 (39)	1.7 (1.4-2.1)	<0.001
Isosorbide mononitrate	89 (12)	56 (7.3)	1.7 (1.2-2.4)	0.006
Omeprazole*	259 (34)	190 (25)	1.6 (1.2-1.9)	<0.001
Allopurinol*	73 (9.5)	49 (6.4)	1.5 (1.1-2.3)	0.027
Gabapentin	97 (13)	67 (8.7)	1.5 (1.1-2.1)	0.015
Aspirin*	194 (25)	144 (19)	1.5 (1.2-1.9)	0.002
Amlodipine	129 (17)	99 (13)	1.4 (1.0-1.8)	0.039
Metoprolol tartrate	209 (27)	167 (22)	1.3 (1.1-1.7)	0.014
B. Within 14 days of the reference date				
Furosemide	11 (1.4)	2 (0.1)	11.4 (2.2-208.2)	0.020
Hydrocodone-acetaminophen*	17 (2.2)	3 (0.4)	5.8 (1.9-25.0)	0.005
Amoxicillin-clavulanate*	10 (1.3)	2 (0.3)	5.6 (1.5-36.7)	0.028
Docusate sodium	11 (1.4)	2 (0.3)	5.4 (1.4-35.0)	0.029
Acetaminophen*	16 (2.1)	3 (0.4)	5.3 (1.8-23.1)	0.008
Metoprolol tartrate	11 (1.4)	3 (0.4)	3.7 (1.1-16.4)	0.047

**Documented as a drug interaction with warfarin in Micromedex®*

associations based on few observations, analyses of drugs in the 30-day period prior to the reference date were limited to those drugs reported for at least 20 of the 1,538 total subjects, while analyses of drug changes in the prior 14 days were limited to those with at least 10 subjects. Results from the logistic regression models were summarized with adjusted odds ratios and confidence limits for each drug of interest. These analyses represent preliminary screening for a large number of potential drug interactions, and the results were not adjusted for multiple comparisons. As such, although the results are presented at the nominal 5% level of statistical significance ($p < 0.05$, per drug), the overall rate of false positive associations may be substantially higher.

Results

The final study population included 769 validated case subjects with major bleeding events and 769 matched control subjects. Each group included 404 males (52.5%), and the mean age in years at the reference date was 76.8 (SD 11.6) and 76.5 (SD 12.3) in the case and control groups, respectively. The study population was almost exclusively Caucasian (only two case subjects and one control subject were identified as African-American), which is consistent with the general population of the health system.

From a total of 115 drugs analyzed from patient electronic medication lists 30 days prior to the major bleeding event reference date, 34 drugs were significantly associated with major bleeding events with concurrent warfarin treatment ($p < 0.05$). Of these 34 drugs, 17 had a previously documented drug interaction with warfarin in the Micromedex® drug information database (Table 1a).[6]

Further analysis of medications initiated within 14 days before the major bleeding event reference date identified six medications from among 12 total medications analyzed that had significant associations with major bleeding events ($p < 0.05$; Table 1b). Three of the six medications have documented drug-drug interactions with warfarin according to the Micromedex® database.[6]

The case group (N=769), on average, had more oral medications on their medication list and higher INRs prior to the reference date than the control group (N=769). The mean total number of drugs identified per patient was 10.5 drugs in the case group (median 10.0; range 1.0-27.0), compared to 8.2 drugs in the control group (median 8.0; range 0.0-22.0; $p<0.001$). The mean number of drugs on the medication list associated with major bleeding (those shown to be statistically significant) in the case group was 3.9 (median 4.0; range 0.0-12.0), compared to 2.4 drugs in the control group (median 2.0; range 0.0-10.0; $p<0.001$). The patients in the case group also had a higher frequency of INRs ≥3.0, including ten patients with an INR ≥9.0. No patients in the control group had an INR >9.0 (Table 2).

TABLE 2. Most Recent INR* Result Prior to the Reference Date

INR Range*	*No. of Case Group Patients (%) N=769*	*No. of Control Group Patients (%) N=769*	*Total (%) N=1538*
≤1.5	29 (3.8)	24 (3.1)	53 (3.4)
1.6-1.9	77 (10.0)	92 (12.0)	169 (11.0)
2.0-3.0	465 (60.5)	556 (72.3)	1021 (66.4)
3.1-3.9	107 (13.9)	74 (9.6)	181 (11.8)
4.0-4.9	52 (6.8)	18 (2.3)	70 (4.6)
5.0-8.9	29 (3.8)	5 (0.7)	34 (2.2)
≥ 9	10 (1.3)	0 (0)	10 (0.7)

*INR = International Normalized Ratio

Discussion

Even though warfarin is closely monitored by many health systems, major bleeding events still occur in patients on warfarin. More attention may be required for a variety of medications that have the potential to interact with warfarin. For starters, when looking at medications that may acutely increase bleeding risk, each of the six medications found to have statistical significance when initiated within 14 days of the reference date could be examined further. For example, although acetaminophen has a documented drug interaction with warfarin, it may be beneficial to place additional focus on assessing potential risk factors, number of medications, patient education and INR monitoring. The same applies for the other documented interactions previously described. As far as the medications considered as undocumented interactions with warfarin in Micromedix®, further research will be needed to determine their clinical significance.[6] Accessing a second drug information database as a standard of practice may also be recommended. For patients that experience a major bleed, not only individual drugs, but also the number of potentially interacting medications should receive attention. The drugs found to be on the patient's medication list 30 days before the major bleeding event should be further analyzed. In the meantime, this study attempts to raise awareness of other medications on the market that may need to be considered when a patient is on warfarin, especially if the patient is on several of the medications in this study.

Of the 34 medications in this study associated with major bleeding events in conjunction with warfarin maintenance therapy, 17 were documented as having drug interactions with warfarin in the Micromedex® drug information database. However, not all drug information databases list the same drug interactions. It is possible there are more drug interactions with warfarin that could increase risk of bleeding than currently documented in the Micromedex® database and using more than one drug knowledge database may be beneficial. Another possible explanation for the apparent discrepancy between the listed drug-warfarin interactions could be due, in part, to procedural and statistical limitations of this study.

When conducting a single institution

medication assessment study with limited demographics (mostly Caucasian patients) and many medications, there is an increased risk for falsely detecting medication interactions. Our ability to statistically evaluate meaningful adverse drug interactions with warfarin was limited by the number of patients exposed to a particular drug and to the observed events attributable to that drug. In a system where a patient's warfarin therapy is closely managed, as in this study, the warfarin dose could be proactively lowered to prevent a thromboembolic event in response to a drug that is well-known to adversely interact with warfarin or increase INR values, perhaps reducing the likelihood that well-recognized drug interactions will show significant associations with bleeding. There is also the chance that the disease state itself could increase a patient's risk for a major bleeding event. For example, anemia is a known risk factor for increased bleeding risk.[7] Another example is furosemide, where the interaction could be due to worsening heart failure increasing the patient's sensitivity to warfarin, thereby increasing bleeding risk.[8] However, these medications can still be important in managing warfarin in that they can serve as an indicator of a compounding drug-disease interaction that may need to be assessed. The number of medications can also represent the number of compounding diseases a patient may have. In addition to this, pharmacogenomics may also impact the patient's bleeding risk. Given the large number of drugs observed, limited sample demographics, and the possibility of confounding variables such as disease state or diet with respect to increasing INR values, we are cautious in our interpretation of statistical analysis for this study.

In addition to statistical limitations, there are also some procedural limitations with this study, including the inability to assess for medication adherence. In addition, some of the case patients may have had a recent non-major bleeding event and therefore been more likely to have been evaluated by a healthcare provider recently and may have received more medications and monitoring in the 14 day period preceding the major bleeding event. When determining if a major adverse bleeding event initially entered into the ACS database was an actual major adverse bleeding event (as defined by a hospitalization, blood transfusion, or death) there is a chance for human error in data entry as well as classification bias. Since only patients with adverse bleeding events treated at Marshfield Clinic were included in this study, all major bleeding events may not have been reported to the Marshfield Clinic ACS if a patient went to an outside facility. Medication changes from non-Marshfield Clinic providers may not be reflected in the medication database, or these providers may not adhere to the same procedures and monitoring practices as Marshfield Clinic ACS personnel.

Future directions include further assessment of individual medications without a currently documented interaction with warfarin and potential confounders based on worsening disease states. Additional drug information databases could be used to further define documented interactions. Also, a goal would be to collect more information and compare disease states between the case and the control group. Due to limited resources and what was accessible in the medical record, we were limited on what characteristics patients could be case matched on. In a future study matching patients based on other bleed risk factors such as HASBLED or ATRIA scores may be beneficial.

Conclusion

Even when patients are closely managed by an anticoagulation service, major bleeding events may still occur due to potentially unknown/unrecognized drug interactions with warfarin. Although the patients in this study were monitored for thromboembolic risk, patients in the case group had somewhat higher INRs as compared to the control group. Further analysis of individual drug interactions with warfarin will determine if current protocols regarding warfarin medication management should be altered in relation to various drugs. The results of this and future studies will be used to review the current protocols for managing warfarin drug interactions.

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