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Ceftriaxone Potentiates Warfarin Activity Greater Than Other Antibiotics in the Treatment of Urinary Tract Infections

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Abstract

Background: The cephalosporin class has been associated with an increased risk of bleeding among elderly patients receiving warfarin. Urinary tract infections (UTI) are the most prevalent infection in elderly patients. *Objective:* To determine the extent of interaction between antibiotics used in the treatment of UTI, particularly specific cephalosporins and warfarin. *Methods:* A retrospective chart review was conducted on chronic warfarin patients with a diagnosis of UTI treated with ceftriaxone, a first-generation cephalosporin, penicillin, or ciprofloxacin. The primary outcome was the comparison of the extent of international normalized ratio (INR) change from baseline between each antibiotic group. *Results:* The ceftriaxone group was found to have a statistically significant higher peak INR value compared to all other studied antibiotics (ceftriaxone: 3.56, first-generation cephalosporins: 2.66, penicillins: 2.98, ciprofloxacin: 2.3; $P = .004$), a statistically significant greater extent of change in INR value (+1.19, +0.66, +0.8, +0.275; $P = .006$), and a statistically significant greater percentage change in INR value when compared to ciprofloxacin (54.4% vs 12.7%; $P = .037$). *Conclusion:* Ceftriaxone interacts with warfarin to increase a patient's INR value more than other commonly administered antibiotics for UTI treatment. Other antibiotics should be preferred for UTI treatment in patients on warfarin.

Keywords

warfarin, ceftriaxone, interaction, antibiotics, cephalosporins

Introduction

Warfarin sodium is the most commonly used oral anticoagulant in the treatment of deep venous thromboembolism, pulmonary embolism, and ischemic cerebrovascular disease, and in the prevention of thromboembolic complications in patients with atrial fibrillation, chronic heart failure, and/or mechanical heart valves.[1] Despite its long and well-established use, warfarin remains a complicated medication for numerous reasons. Warfarin has a narrow therapeutic index, has numerous drug and food interactions, and displays significant inconsistency in dose response based on many patient characteristics. Due to this, warfarin requires frequent monitoring and dose alterations to minimize subtherapeutic and supratherapeutic international normalized ratio (INR) values and possible serious complications.

One frequent reason warfarin therapy can become subtherapeutic or supratherapeutic is drug interactions.[1-3] In a systematic literature review of warfarin and its drug and food interactions, many anti-infectives were described as having a high probability of potentiating the effect of warfarin.[2] This interaction can occur via multiple mechanisms, with the 2 most frequently cited being the inhibition of cytochrome p450 (CYP) isozymes, particularly CYP2C9 and CYP3A4, and the disruption of intestinal normal flora. These interactions result in decreased warfarin metabolism and reduction in organic vitamin K synthesis respectfully, both contributing to increases in INR values and a significant increase in bleeding risk.[3,4]

In a recent study by Baillargeon et al, it was found that any anti-infective use was associated with a 2-fold increased risk of bleeding within 15 days of anti-infective administration in elderly chronic warfarin users.[4] The authors determined that the cephalosporin class was associated with the third highest risk of bleeding, behind azole antifungals and sulfamethoxazole/trimethoprim and ahead of fluoroquinolones. To date, there are no studies showing a significant interaction between cephalosporins and warfarin, and only case reports examined such interactions.[5] Currently, there is no literature examining the bleeding risk and extent of interaction between specific cephalosporins or generations of cephalosporins and concurrent warfarin use.

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Among elderly hospitalized patients (greater than or equal to 65 years of age), urinary tract infections (UTIs) are the most common infection diagnosed, accounting for 25% of all infections in this population.[4,6] Because the elderly are also the largest demographic of warfarin users,[1] the coadministration of warfarin and antibiotics for UTI treatment is quite common and potential interactions could be overlooked.[4,6] Cephalosporins, such as cefazolin, cephalexin, and ceftriaxone, are frequently used for the treatment of UTI in our hospital. Therefore, the objective of this study is to compare the extent of interaction between concurrent warfarin use and antibiotics for the treatment of UTI, most notably specific agents within the cephalosporin class.

Methods

A retrospective chart review of patients was conducted at a community teaching hospital between June 1, 2011, and September 30, 2012. Patients were included in this study if they were admitted as an adult inpatient, had a diagnosis of UTI, and were receiving warfarin for any indication prior to admission (based on the admission medication reconciliation). Patients less than 18 years of age, patients who were not receiving warfarin prior to hospital admission, and patients who had an active bleeding event at the time of antibiotic initiation were excluded from this study.

Demographics and laboratory data on study participants collected from the patient chart included patient's age, weight, gender, race, body mass index, indication for warfarin use, goal INR range, INR values during extent of hospital stay, length of hospital stay, alkaline phosphatase, serum creatinine, and creatinine clearance.

Included patients were divided into 4 groups based on the antibiotic used to treat the UTI: ceftriaxone, first-generation cephalosporins (including cefazolin or cephalexin), penicillins (including ampicillin/sulbactam, amoxicillin/clavulanate, or piperacillin/tazobactam), or ciprofloxacin. If a patient's antibiotic was changed during the course of treatment, due to susceptibility reports, physician preference, or other reasons, the original antibiotic was used to define the patient's treatment group. INR values were recorded on the date of admission (or earliest documented), date of antibiotic start, and date of peak INR value during the length of stay. Total INR change and percentage of change in INR value from day one of antibiotic use to the peak INR value were compared for each study group. Additionally, bleeding events, defined as gastrointestinal, cerebrovascular, or other, were identified in each study group through a chart note review.

Statistics

Repeat measures analysis of variance (ANOVA) was used to determine if there was a significant difference in the primary outcome among the different antibiotic groups. The Fisher's exact test was used to compare the incidence of bleeding rates between the groups. To determine if there was a statistically significant difference in patient characteristics between the antibiotic groups, patient demographic variables and baseline data were compared using the Bonferroni's post hoc test in ANOVA, Kruskal-Wallis test, Fisher's exact test, and/or Pearson chi-square test, as appropriate. Continuous variables were compared using the Kruskal-Wallis test and reported as a median and interquartile range (IQR). Statistical analysis was conducted using SPSS 20.0 (IBM SPSS, Chicago, Illinois), and a P value of $<.05$ was considered statistically significant.

Results

There were a total of 209 patients who were screened and found to have a diagnosis of a UTI and were on warfarin at some point during their hospital admission. From those 209 patients, a total of 89 patients were excluded. There were 61 patients who were excluded for a lack of active warfarin treatment before admission and 16 patients who had a diagnosis of a bleed before antibiotic administration. Additionally, 7 patients had to be excluded due to a lack of laboratory data, and 5 patients were excluded who were never started on an antibiotic during their hospital stay. In total, there were 120 patients who met inclusion criteria and were analyzed in the study: 27 were treated with ceftriaxone, 14 with a first-generation cephalosporin, 57 with a penicillin, and 22 with ciprofloxacin.

Table 1 presents the demographics and baseline data of the 120 analyzed patients in the study. No demographics or baseline data were found to have any statistical differences among the 4 antibiotic treatment groups. Overall, the majority of patients were on warfarin for atrial fibrillation and had a goal INR therapeutic range of between 2 and 3. Before antibiotic initiation, it was found that only 45.8% of all patients were within their documented therapeutic range. Although not statistically significant, the ceftriaxone group did have the highest percentage of patients within therapeutic range at baseline at 55.6%. The median baseline INR value of the 120 patients was found to be 1.97 (IQR 1.31-2.63).

The 4 different antibiotic treatment groups were also compared for coadministration of other drug–drug interactions with warfarin. These included strong CYP2C9 and CYP3A4 inhibitors, selective serotonin reuptake inhibitors, selective norepinephrine reuptake inhibitors, and corticosteroids. There was not found to be any statistically significant differences between the antibiotic treatment groups in the coadministration of additional interacting medications with warfarin that could have confounded the results.

Table 2 displays the primary and secondary objective patient data after antibiotic initiation for each of the antibiotic treatment groups. Among all patients, the median number of days from antibiotic initiation to peak INR value was 2 days (IQR 1-3), and there was not found to be a statistically significant difference between any of the antibiotic treatment groups in this aspect. The median peak INR value of all patients was found to be 3.09 (IQR 2.08-4.1). When comparing the peak INR values, the ceftriaxone treatment group had a statistically significant higher peak when compared to the first-generation

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Table 1. Demographics and Baseline Patient Data.

	CTX	CEF	PCN	CIP	*P* value
Age, years	79	75	75	78	.939
Length of Stay, days	8	9	7	6	.366
Indication,[a] % of patients					
Afib	59.3	57.1	48.1	33.3	.399
VTE	25.9	7.1	35.2	42.8	
Heart valve	11.1	21.4	1.9	9.5	
Goal INR,[b] % of patients					
2-3	81.5	92.9	91.2	86.4	.684
2.5-3.5	7.4	7.1	3.5	13.6	
Within TR, % of patients	55.6	35.7	49.1	31.8	0.322
INR at antibiotic initiation, (IQR)	2.3 (1.48-2.91)	1.83 (1.39-2.49)	1.92 (1.54-2.86)	1.82 (1.34-2.5)	.603
Other warfarin interactive medications, % of patients	48.1	71.4	49.1	50	.484

Abbreviations: CTX, ceftriaxone; CEF, first-generation cephalosporins; PCN, penicillins; CIP, ciprofloxacin; AFib, atrial fibrillation; VTE, venous thromboembolism; INR, international normalized ratio; TR, therapeutic range; IQR, interquartile range.
[a]Remaining percent "other."
[b]Remaining percent per physician preference.

Table 2. Analyzed Results After Antibiotic Administration.

	CTX	CEF	PCN	CIP	*P* value
Days to peak INR (IQR)	3 (1-5)	2 (0.75-3)	2 (1-5)	1.5 (.3-2.5)	.138
Peak INR (IQR)	3.56 (2.91-5.2)	2.66 (1.79-3.75)	2.98 (2.16-4.07)	2.3 (1.87-3.34)	.004
Total INR increase (IQR)	1.19 (0.82-2.45)	0.66 (0.01-1.17)	0.8 (0.13-1.5)	0.275 (0-1.07)	.006
INR percentage change[a] (IQR)	54.4 (23.9-119)	39.6 (0.76-77.2)	42.8 (6.04-81.6)	12.7 (0-49.7)	.037[b]
Bleed, % of patients	0	0	4 (8)	0	.526

Abbreviations: CTX, ceftriaxone; CEF, first-generation cephalosporins; PCN, penicillins; CIP, ciprofloxacin; INR, international normalized ratio; IQR, interquartile range.
[a]Percentage change from baseline: ([peak INR value – baseline INR value] / baseline INR value) × 100.
[b]Statistical significance only between ceftriaxone and ciprofloxacin.

cephalosporins, penicillins, and ciprofloxacin treatment groups (3.56, IQR 2.91-5.2; 2.66, IQR 1.79-3.75; 2.98, IQR 2.16-4.07; 2.3, IQR 1.87-3.34, respectively; $P = .004$). The ceftriaxone treatment group was also found to have a greater total increase in INR value from baseline compared to all other antibiotic treatment groups (1.19, IQR 0.82-2.45; 0.66, IQR 0.01-1.17; 0.8, IQR 0.13-1.5; 0.275, IQR 0-1.07, respectively; $P = .006$). We also assessed the percentage of INR change from baseline and found that the ceftriaxone treatment group had a greater percentage change than all other treatment groups but was only found to be statistically significant when compared to ciprofloxacin (54.4 vs 12.7; $P = .037$). Four bleeding events were observed after antibiotic administration, all of which occurred in the penicillin treatment group, but was not found to have any statistical significance.

Discussion

Among the examined treatments for UTIs, ceftriaxone was the most likely to significantly increase the INR value in chronic warfarin patients. Presently, there is limited literature addressing this interaction between ceftriaxone and warfarin, but our finding is consistent with Clark et al's report that ceftriaxone may have a significant potentiating interaction with warfarin.[5]

The mechanism of interaction between ceftriaxone and warfarin is currently not well defined. It is known, however, that antibiotics can interfere with the normal intestinal flora that produce a substantial amount of vitamin K. The recommended daily allowance for vitamin K for adults is 90 μg.[7] One small study of health volunteers determined that approximately 1.6 mg of menaquinones (bacteria-synthesized vitamin K) were produced by the colonic bacteria.[8] Ceftriaxone undergoes an estimated 33% to 67% biliary excretion, generating relatively high concentrations in the intestine.[9] This pharmacokinetic trait provides ceftriaxone the ability to interfere with the intestinal normal flora to a larger extent than primarily renally excreted antibiotics, thus causing a greater reduction in the organic production of vitamin K.

In this study, patients started on ciprofloxacin had the least change in INR value. This finding could be considered controversial considering some previous literature has described a greater warfarin-potentiating effect of ciprofloxacin than shown here. In a literature review by Holbrook et al, the authors categorized ciprofloxacin as 1 of 8 anti-infectives with a highly probable association with a warfarin-potentiating interaction.[2] Conversely, a literature review by Carroll et al on potential interactions between warfarin and 3 separate fluoroquinolones concluded that ciprofloxacin did not display consistent

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increases in anticoagulant effects during coadministration.[10] In view of these inconsistencies and the results of our study, this relationship should be investigated further in future studies.

The results of this study may have been influenced by some limitations. First, the study was a retrospective design, leaving a greater opportunity that the results were due to chance. Second, a greater than expected percentage of patients were not within therapeutic INR range for warfarin therapy at baseline. In consequence, changes in patients' INR value, due factors prior to admission such as recent changes in warfarin dose or noncompliance, could have been attributed to attaining therapeutic range. It should be recognized, though, that the ceftriaxone group did have the highest baseline INR and the greatest percentage of patients within their therapeutic range at baseline (2.3% and 55.6%, respectively). Therefore, this limitation most likely did not have much effect on the significant INR increase observed within the ceftriaxone group. Third, INR values were not able to be collected after patient's discharge from the hospital. This limited the overall amount of data that were able to be collected in our study. Furthermore, findings by Baillargeon et al determined that any anti-infective coadministered with warfarin therapy can increase a patient's risk of bleeding for at least 15 days.[4] Our median length of stay was only 7 days; therefore, additional warfarin potentiation could have been missed in patients after discharge. Finally, warfarin dosing changes were not included. Consequently, the intensity of anticoagulation therapy and the occurrence of any dose increases or reductions before antibiotic administration that could have influenced INR value changes were not analyzed.

Conclusion

Utilization of any antibiotic has been shown to potentiate the effect of warfarin, putting a patient at risk of bleeding events. Based on our findings, clinicians should consider avoiding ceftriaxone for the treatment of UTIs in chronic warfarin patients and prescribe antibiotics with established lesser degree of warfarin-potentiating effects. First-generation cephalosporins could be recommended as a better option within the cephalosporin class as appropriate to regional susceptibility data. If such therapeutic substitution is not possible, then close monitoring of INR, both inpatient and outpatient, is warranted.

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