BRIEF REPORT: The Risk of Overanticoagulation with Antibiotic Use in Outpatients on Stable Warfarin Regimens

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BACKGROUND: Medication interactions account for a significant proportion of overanticoagulation in warfarin users. However, little is known about the incidence or degree of interaction with commonly used oral antibiotics.

OBJECTIVE: To investigate the incidence and degree of overanticoagulation associated with commonly used oral antibiotics.

DESIGN: Retrospective cohort study of patients using warfarin who initiated an antibiotic (azithromycin, levofloxacin, or trimethoprim/sulfamethoxazole (TMP/SMX)) or terazosin for clinical indications between January 1998 and December 2002. The incidence of international normalized ratio (INR) elevation and the degree of change and bleeding events after institution of either medication type was recorded.

SUBJECTS: Patients at a university-affiliated Veteran's Affairs Medical Center.

RESULTS: The mean change in INR was -0.15 for terazosin, 0.51 for azithromycin, 0.85 for levofloxacin, and 1.76 for TMP/SMX. These mean INR changes in the antibiotic groups were all statistically different from the terazosin group. The incidence of supratherapeutic INR was 5% for terazosin, 31% for azithromycin, 33% for levofloxacin, and 69% for TMP/SMX. The incidence of absolute INR >4.0 was 0% for terazosin, 16% for azithromycin, 19% for levofloxacin, and 44% for TMP/SMX.

CONCLUSIONS: Among acutely ill outpatients, oral antibiotics (azithromycin, levofloxacin, and TMP/SMX) increase the incidence and degree of overanticoagulation.

KEY WORDS: warfarin; overanticoagulation; drug interaction; azithromycin; levofloxacin; trimethoprim/sulfamethoxazole.
DOI: 10.1111/j.1525-1497.2005.0136.x
J GEN INTERN MED 2005; 20:653–656.

The benefits of warfarin are well established but offset by the risk of major hemorrhage, which occurs at 2.2% rate per year, with a 13% case fatality rate.[1] Bleeding may occur at therapeutic international normalized ratios (INR) but is much more likely to occur as the INR rises beyond therapeutic levels.[2,3] Antibiotic interactions are recognized as a major cause of overanticoagulation.[4–8] However, few data on the incidence of this interaction and the degree to which it induces changes in the INR are available, so we investigated this interaction in a population of acutely infected, otherwise stable outpatients for 3 commonly used antibiotics—azithromycin, levofloxacin, and trimethoprim/sulfamethoxazole (TMP/SMX).

METHODS

We conducted a retrospective cohort study of patients with stable warfarin doses and INRs who received a prescription for terazosin, azithromycin, levofloxacin, or TMP/SMX for clinical indications between January 1998 and December 2002 at a university-affiliated Veteran's Affairs Medical Center. Terazosin was chosen as our control because of its lack of interaction with warfarin.[9] Participants were included if 2 inclusion INRs (the last occurring within 30 days prior to the introduction of the antibiotic/terazosin) were within $\pm$ 0.2 of the therapeutic range and within 0.5 of each other, and a repeat INR was drawn within 3 to 15 days after commencement of any of the antibiotic medications. The time frame was extended to 30 days for terazosin, as INRs are generally not followed as closely after commencing it. Subjects were excluded if they had a change in warfarin dosing or initiated or changed a scheduled medication that is known to interact with warfarin during or after collection of their inclusion INRs. As needed medications were allowed if the medication was not commonly felt to interact with warfarin based on an accepted text of drug interactions.[10] Patients were included twice for a second episode if all of the above criteria were met.

Data Collection

Information was collected from an electronic medical record on the highest INR during the follow-up period, the change in INR from baseline, any complications of extended INR, use of vitamin K reversal or transfusion with fresh-frozen plasma or red blood cells, and hospitalization secondary to overanticoagulation. Additional data included age, race, gender, medication use, and the presence of fever, anorexia, diarrhea, and liver or renal failure.

STATISTICS

Data are presented as means and ranges. Groups were compared using χ^2 testing and Fisher's exact test for categorical variables (Statxact 3.0, Cytel Software Corp., Boston, Mass) and analysis of variance for continuous variables with least statistical difference method adjustment for multiple comparisons (SPSS 12.0, SPSS Inc., Chicago, Ill).

Drs. Glasheen, Fugit, and Prochazka have no financial disclosures, and have no conflicts of interest to report for this article or this research.

Presented at the Society of Hospital Medicine National Meeting, San Diego, CA, April 1, 2003.

Dr. Glasheen was affiliated with the Department of Medicine, Division of General Internal Medicine, at the Denver VA Medical Center, University of Colorado Health Science Center, Denver, CO, during the data collection phase of this research.

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Received for publication December 14, 2004
Accepted for publication February 15, 2005

RESULTS

We identified 333 prescriptions for terazosin in 333 patients, 273 prescriptions for azithromycin in 158 patients, 370 prescriptions for levofloxacin in 258 patients, and 151 prescriptions for TMP/SMX in 120 patients. Initially 43, 35, 41, and 24 terazosin, azithromycin, levofloxacin, and TMP/SMX patients, respectively, were included and brought to full author review. The group then carefully reviewed each remaining patient, collecting extra data where needed until all exclusions were made as indicated. Nine patients in the terazosin group had follow-up INRs on or before day 15 and an additional 11 patients had INRs drawn between days 15 and 30. Thirty-two azithromycin, 27 levofloxacin, and 16 TMP/SMX patients were included in the trial (Table 1).

There were no differences in outcomes in the terazosin data analyzed at day 15 or 30, so the latter was used in all further analysis. The median time to follow-up was 17.5 (terazosin), 7 (azithromycin), 6 (levofloxacin), and 6 (TMP/SMX) days. Men constituted 97% of all patients and the mean age for all groups was 70 years old. There were no differences in the indications for warfarin use (P=.779). Azithromycin and TMP/SMX were prescribed primarily for pulmonary infections while levofloxacin was used most often for urinary tract infections. Terazosin was nearly always prescribed for symptomatic benign prostatic hypertrophy. Chronic renal disease was common while chronic liver disease was not. The mean creatinine in the patients with renal failure was 2.3 mg/dL for azithromycin, 2.0 mg/dL for levofloxacin, and 2.5 mg/dL for TMP/SMX.

A graded increase in both the incidence and degree of warfarin interaction from terazosin to azithromycin to levofloxacin to TMP/SMX was found (Table 2). Overall, the mean INR increased significantly for all 3 antibiotics compared with terazosin. While the INR decreased slightly for terazosin (-0.15), mean increases in INR of 0.51, 0.85, and 1.76 were seen in the azithromycin, levofloxacin, and TMP/SMX groups. Elevations in INR beyond therapeutic levels were seen in 5% (terazosin), 31% (azithromycin), 33% (levofloxacin), and 69% (TMP/SMX) of patients. The P-value for all 3 antibiotics versus terazosin was $<.05$. More clinically significant elevations of INR, denoted as elevations beyond 4, were seen in 0% (terazosin), 16% (azithromycin), 19% (levofloxacin), and 44% (TMP/

Table 1. Demographic Characteristics and Clinical Features

	Terazosin		Azithromycin	Levofloxacin	TMP/SMX
	15 d	30 d			
Number included	9	20	32	27	16
Mean age (y)	70	71	72	69	68
Median age (y)	75	72	74	69	67
Male (%)	100	100	94	100	100
Mean warfarin dose (mg/wk)	34.4	33.2	29.9	37.0	27.3
Acute renal disease					
Creatinine >1.3 mg/dL	1	1	0	1	0
Creatinine (mean)					
pts. with ARF (mg/dL)	(1.7)	(1.7)		(2.8)	
Chronic renal disease					
Creatinine >1.3 mg/dL	0	3	9	10	3
Creatinine (mean, range)					
pts. with CRF (mg/dL)		(1.8, 1.6–3.1)	(2.3, 1.4-5.8)	(2.0, 1.4-5.8)	(2.5, 1.5-4.3)
Acute liver disease					
Albumin <3.0 g/dL	0	0	0	0	0
ALT >65 u/L	0	0	0	0	1
Total bilirubin >1.5 mg/dL	0	0	0	0	0
Chronic liver disease					
Albumin <3.0 g/dL	0	0	2	0	0
ALT >65 u/L	1	1	1	0	1
Total bilirubin >1.5 mg/dL	0	0	1	0	0
Fever	0	0	0	0	0
Anorexia	0	0	0	0	0
Diarrhea	0	0	1	1	0
Warfarin indication	**No.**	**No (%)**	**No (%)**	**No (%)**	**No (%)**
Afib/Aflutter	3	10 (50)	12 (38)	10 (37)	6 (38)
Thrombosis	4	4 (20)	6 (19)	9 (33)	6 (38)
Valvular	1	4 (20)	10 (31)	6 (22)	3 (19)
CVA/TIA	0	1 (5)	4 (13)	1 (4)	1 (6)
CAD/CHF	1	1 (5)	0 (0)	1 (4)	0 (0)
Antibiotic indication			**No (%)**	**No (%)**	**No (%)**
Pulmonary			25 (78)	7 (26)	10 (63)
UTI/Epididymitis			0 (0)	14 (52)	1 (6)
URI/Sinusitis/Otitis/Pharyngitis			6 (19)	2 (7)	0 (0)
Other			1 (3)	4 (15)	5 (31)

TMP/SMX, trimethoprim/sulfamethoxazole; ARF, acute renal failure; CRF, chronic renal failure; CVA, cerebrovascular accident; TIA, transient ischemic attack; CAD, coronary artery disease; CHF, congestive heart failure; UTI, urinary tract infection; URI, upper respiratory infection; ALT, alanine aminotransferase.

Table 2. Effect of Various Antibiotics on Stable INRs in Acutely Ill Outpatients

	N	Median f/u (d)	Mean INR change	INR increase ≥ therapeutic (%)	INR increase ≥ 1 (%)	INR increase ≥ 2 (%)	Absolute INR ≥ 4 (%)	Absolute INR ≥ 5 (%)
Terazosin	20	17.5	−0.145	5	0	0	0	0
Azithromycin	32	7	0.51*	31*	19	9	16	3
Levofloxacin	27	6	0.85†	33*	30†	11	19	11
TMP/SMX	16	6	1.76‡	69‡	56‡	38†	44†	31*

*P *value*<.05 *versus terazosin.*
†P *value*<.01 *versus terazosin.*
‡P *value*<.001 *versus terazosin.*
TMP/SMX, trimethoprim/sulfamethoxazole; INR, international normalized ratio.

SMX). The *P*-value was significant for TMP/SMX versus terazosin, with a nonsignificant trend between both azithromycin and levofloxacin versus terazosin. Even more significant rises in INR were consistently seen with TMP/SMX, with 38% showing a mean change in INR of 2 or more points and 31% of subjects showing a rise in INR of ≥ 5. Thirteen percent of the TMP/SMX patients experienced an adverse bleeding event. There were no documented bleeding episodes in the other groups.

DISCUSSION

Our data show a significant increase in the incidence of overanticoagulation when azithromycin, levofloxacin, or TMP/SMX was added to chronic warfarin therapy in patients who were acutely ill. Prior studies are limited because they were case reports, used only healthy volunteers, had an inadequate control group, or did not have a denominator to calculate incidence. Consequently, these studies mention very little about the risk of overanticoagulation in an individual patient treated with an antibiotic, rendering it difficult to incorporate risk–benefit ratios into the decision analysis of which antibiotic to use in anticoagulated patients and how to prescribe follow-up.

Previously, 2 retrospective studies found no significant differences in INR after the initiation of azithromycin for clinical indications compared with terazosin[9] or felodipine.[11] However, only 19 of 43 azithromycin subjects had a follow-up INR within 15 days, with the remaining 24 patients postantibiotic INR occurring on day 26 (mean). It is possible that INR levels drawn after day 15 could miss important antibiotic interactions.

Prospective studies have suggested that anticoagulated patients can safely use the newer quinolone antibiotics.[12–15] However, they have a small sample size (mean 13.8 patients), use nonacutely ill subjects, and lack proper randomization. Yamreudeewong et al.[16] completed a study of 18 warfarin users who required levofloxacin daily for 5 to 10 days for infectious indications. No difference was found in the mean INR change before and at the first follow-up (median follow-up, day 5 ± 1.29 days). However, the study had high levels of patient withdrawal and numerous dose adjustments such that only 5 patients completed the entire study without a dose adjustment. Overall, 44% of the patients saw their INR increase beyond therapeutic levels, 17% increased more than 1 point, 11% increased their INR to a level greater than 4.0, and 44% required a dosing change because of an elevated INR.[17] These results suggest that a levofloxacin–warfarin interaction exists and are congruent with our findings.

It is well known that sulfa-based antibiotics interact with warfarin, but the incidence has not been adequately studied.[5] Comparing 300 outpatients who presented with INR values greater than 6.0 with a randomly selected matched control group, Penning-van Beest found that TMP/SMX was 1 of only 2 drugs that conferred an increased risk of overanticoagulation.[6] O'Reilly and colleagues evaluated 11 subjects who were neither acutely ill nor on chronic warfarin and concluded that TMP/SMX potentiates the prothrombin effect of warfarin.[18]

Our study has several strengths. We eliminated patients who did not have both a stable warfarin dose and a stable level of anticoagulant intensity and limited the follow-up period to 3 to 15 days, when it is most likely that an antibiotic interaction would be observed. The drugs were used for clinical indications and at standard doses. We excluded patients who initiated other potentially interacting medications. We made every effort to identify factors that may affect coagulability and found no significant differences between the groups in the rates of fever, anorexia, or chronic liver disease. Chronic renal disease was seen more frequently in the azithromycin and levofloxacin groups than the TMP/SMX and terazosin groups; however, the significance of this is unknown but is likely to be minimal. Finally, we utilized a negative (terazosin) and positive (TMP/SMX) control to confer validity to our findings. Terazosin is known not to interact with warfarin, while TMP/SMX has a well-described interaction.[5,9] Anchoring our study on both the negative and positive ends strengthens our conclusions regarding the interaction between azithromycin, levofloxacin, and warfarin.

Our study also has several significant limitations. We could not control for patient medication compliance or use of over-the-counter medications. Also, we are unable to differentiate the role that the medication played in the interaction from that of the illness itself. Ultimately, however, this distinction is academic as clinicians are primarily interested in the overall effect of the medication within the context of the illness for which it is commonly used.

CONCLUSION

Among acutely ill outpatients, the use of the oral antibiotics azithromycin, levofloxacin, and TMP/SMX increases both the incidence and degree of overanticoagulation. Close monitoring of INRs after initiation of any of these 3 antibiotics is strongly recommended.

Dr. Glasheen certifies that he has had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All above-stated authors have contributed to the design, execution, analysis, and writing of this manuscript.

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