J Thromb Thrombolysis (2008) 26:44–48
DOI 10.1007/s11239-007-0164-z

Impact of preemptive warfarin dose reduction on anticoagulation after initiation of trimethoprim-sulfamethoxazole or levofloxacin

Abrar Ahmed · John C. Stephens · Carol A. Kaus · William P. Fay

Published online: 6 November 2007

Abstract *Background* Antibiotics can potentiate warfarin anticoagulation. While preemptive warfarin dose reduction (DR) upon initiation of antibiotics has been advocated by experts, there are no published data regarding the efficacy of this strategy vs. the conventional strategy of not changing warfarin dose and carefully following international normalized ratio (INR) results. *Methods and Results* We compared the efficacy of preemptive 10–20% DR vs. no change in warfarin dosing in 40 chronically anticoagulated patients initiating trimethoprim-sulfamethoxazole (TMP-SMX) or levofloxacin. Eighteen patients received preemptive warfarin DR and 22 control patients underwent no change in warfarin dosing. There was no difference between the DR and control groups in the mean INR before beginning antibiotic therapy (2.53 ± 0.12 vs. 2.52 ± 0.11; $P > 0.9$). Mean interval between initiation of antibiotic and next INR was 5.1 ± 0.4 vs. 4.7 ± 0.5 days for DR vs. control patients, respectively ($P > 0.5$). For both TMP-SMX and levofloxacin, patients managed with a preemptive warfarin DR strategy did not exhibit a statistically significant change in the INR after initiating antibiotic therapy. In contrast, for each antibiotic, control group patients exhibited a significant increase in mean post-antibiotic INR compared to mean pre-antibiotic INR, though the effect was more pronounced in patients treated with TMP-SMX than with levofloxacin. Of DR group patients who were treated with TMP-SMX, none (0/8) developed a subtherapeutic INR, while 40% (4/10) of levofloxacin-treated patients developed a sub-therapeutic INR. Supra-therapeutic INR results led to transient interruption of warfarin dosing in 2 patients (11%) in the DR group vs. 12 patients (55%) in the control group ($P = 0.007$). *Conclusions* Prophylactic warfarin DR of 10–20% is effective in maintaining therapeutic anticoagulation in patients initiating TMP-SMX. An expectant strategy consisting of no change in warfarin dosing with short-term INR follow-up appears reasonable in patients treated with levofloxacin.

Keywords Anticoagulation · Warfarin · Antibiotics

Introduction

Several antibiotics can alter warfarin metabolism and increase systemic anticoagulation [1–6]. When a chronically anticoagulated patient is started on an antibiotic recognized to potentiate warfarin, a common clinical approach is to check the patient's International Normalized Ratio (INR) within several days. This strategy allows for a prompt alteration in warfarin dosing in the event that systemic anticoagulation is altered by the antibiotic. For some antibiotics, such as trimethoprim-sulfamethoxazole (TMP-SMX), the INR can increase to dangerously high levels within only three days after initiation of therapy [7], which has prompted some experts to recommend a preemptive reduction in warfarin dose at the time some antibiotics are started—i.e. even before follow-up INR testing is performed [8]. However, there are no data in the medical literature regarding the effectiveness of preemptive warfarin dose reduction (DR) in maintaining a constant level of anticoagulation, the frequency with which this strategy

A. Ahmed (✉) · W. P. Fay
Department of Internal Medicine, School of Medicine, University of Missouri-Columbia, MA406, DC043.00, One Hospital Drive, Columbia, MO 65212, USA
e-mail: ahmedab@health.missouri.edu

J. C. Stephens · C. A. Kaus
University of Michigan Medical School, Ann Arbor, MI, USA

leads to sub-therapeutic INR results, or how preemptive warfarin DR compares to the standard approach of maintaining the same warfarin dose and carefully following the INR. To address these issues, we identified a cohort of patients managed with a preemptive warfarin DR strategy upon starting either TMP-SMX or levofloxacin, two commonly employed antibiotics with the potential to potentiate warfarin anticoagulation [7–15]. We compared their short-term anticoagulation outcomes to those of a group of patients managed without preemptive warfarin DR.

Methods

Patients

The study was approved by the University of Michigan Institutional Review Board. All patients were managed by the University of Michigan Health System Anticoagulation Management Service (AMS), a physician-supervised, nurse-staffed, telephone-based service that utilizes standardized algorithms to manage warfarin therapy. Patients in the study were identified between August 2002 and March 2004. During this period of time all patients received explicit instructions (delivered during new patient education sessions, and at all follow-up telephone and written interactions with patients) to contact the AMS if any new medication was prescribed, particularly an antibiotic. In addition, AMS nurses contacted patients after each INR result, at which time the nurse inquired whether the patient had recently started or was about to start any new medication, and whether the patient had experienced any bleeding or thrombosis symptoms. The names of all patients identified as receiving either TMP-SMX or levofloxacin during the period of time described above were confidentially recorded for subsequent analysis. A patient was considered for preemptive 10–20% warfarin DR only if he/she had not yet started the antibiotic, or had been receiving it for ≤48 h. The clinical decision of whether or not to make a preemptive warfarin DR was not a randomized process. Since some literature available at the time recommended preemptive warfarin DR for some antibiotics [8], while other literature recommended no changes in warfarin dosing with careful INR monitoring [7], nurse discretion was allowed in making this decision. Patients who received a preemptive warfarin DR were instructed to resume their normal daily warfarin schedule the day after stopping antibiotic therapy. Only patients with (1) stable anticoagulation preceding antibiotic therapy (defined as having ≥2 consecutive INR results within 0.3 units of the therapeutic range during the 6 weeks preceding initiation of antibiotic therapy), and (2) follow-up INR testing within seven days after starting antibiotic therapy, were included in the study. Patients were excluded if they had received another antibiotic within the 4 weeks before starting either TMP-SMX or levofloxacin. All patients received daily doses of antibiotic for a minimum of seven days.

Statistical methods

Continuous data, expressed as mean ± 1 standard deviation, were examined using the paired *t*-test and Wilcoxon rank test. Categorical variables were compared using the Chi-square test or the Fisher Exact test, as appropriate. All analyses were performed using SAS, version 8, Cary, NC.

Results

The warfarin DR group consisted of 18 patients and the control group consisted of 22 patients. Seventeen patients received TMP-SMX and 23 patients received levofloxacin. There were no significant differences between the DR group and the control group with respect to gender, age, weekly warfarin dose, target INR, and frequency of use of each antibiotic (Table 1).

The mean value of the most recent INR before beginning antibiotic therapy did not differ significantly between the preemptive warfarin DR group and the control group (2.53 ± 0.12 vs. 2.52 ± 0.11, respectively; $P > 0.9$), nor did the mean number of days after initiating antibiotic therapy that the INR was first checked (5.1 ± 0.4 vs. 4.7 ± 0.5, respectively; $P > 0.5$). In the DR group, the TMP-SMX-treated patients ($n = 8$) had a mean 16.3 ± 2.8% reduction in daily warfarin dose, and levofloxacin-treated patients ($n = 10$) had a mean 16.2 ± 1.8% reduction in daily warfarin dose ($P = 0.95$). For both TMP-SMX and levofloxacin, patients managed with a preemptive warfarin DR strategy did not exhibit a statistically significant change in the INR after initiating antibiotic therapy (Fig. 1). In contrast, for each antibiotic, control group patients exhibited a significant increase in mean post-antibiotic INR compared to mean pre-antibiotic INR, though the effect was more pronounced in patients treated with TMP-SMX than with levofloxacin (Fig. 1). Comparison of pre- and post-antibiotic INR results for each patient revealed that prophylactic warfarin DR generally led to "flat" INR responses for both TMP-SMX and levofloxacin (Fig. 2A). In contrast, all TMP-SMX-treated patients in the control group exhibited a post-antibiotic INR result that was higher than the pre-antibiotic INR value, while most levofloxacin-treated patients in the control group exhibited a relatively flat INR response (Fig. 2B). Of TMP-SMX-treated patients, 25% (2/8) in the DR group developed an

Table 1 Baseline patient characteristics

Patient characteristics	Dose-reduction group ($n = 18$)	Control group ($n = 22$)	*P*-value
Demographics			
Male	7 (39)	4 (18)	0.17
Female	11 (61)	18 (82)	0.17
Age (years)	70 ± 10	66 ± 19	0.64
Weekly warfarin dose (mg)	35 ± 18	35 ± 16	0.78
Target INR range			
2–3	17 (94)	20 (91)	0.613
Other	1 (5)	2 (9)	
Anticoagulation diagnosis			
Atrial fibrillation	7 (39)	6 (27)	0.44
DVT/PE	4 (22)	9 (41)	0.21
Prosthetic valve	3 (17)	3 (14)	1.00
Hypercoagulable state	4 (22)	2 (9)	0.38
Other	0 (0)	2 (9)	0.49
Antibiotic			
TMP-SMX	8 (44)	9 (41)	0.80
Levofloxacin	10 (56)	13 (59)	0.99

Numbers in parentheses represent % of total patients for each group

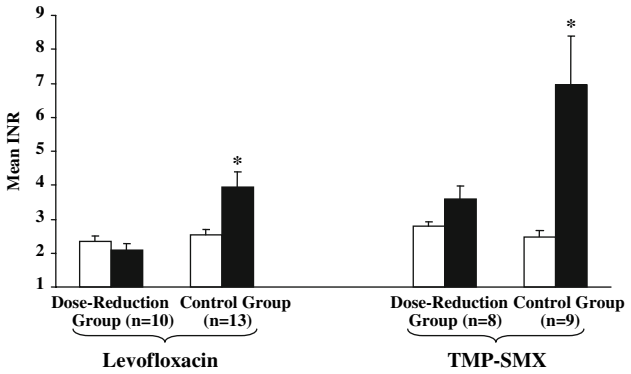

Fig. 1 Mean pre-antibiotic (empty bars) and post-antibiotic (black bars) INR values for the warfarin DR and control groups, for TMP-SMX- and levofloxacin-treated patients. *$P < 0.02$ vs. corresponding pre-antibiotic INR

INR >4.0, compared to 88.9% (8/9) in the control group ($P < 0.02$). None of 8 patients (0%) given a warfarin DR developed an INR $\geq$ 6, while 4 of 9 control patients (44%) did ($P = 0.08$), with values ranging from 7.1 to 17.4. No patients in either the DR or control groups developed a subtherapeutic INR. Of levofloxacin-treated patients, none (0/10) in the DR group developed an INR >4.0, compared to 38.5% (5/13) in the control group ($P < 0.05$). However, the incidence of INR values $\geq$6.0 did not differ significantly between the DR vs. control groups (0/10 vs. 1/13, respectively; $P = 0.99$), and 40% of patients (4/10) in the DR group developed a subtherapeutic INR, compared to none of the control group patients (0/13; $P < 0.03$). Of the

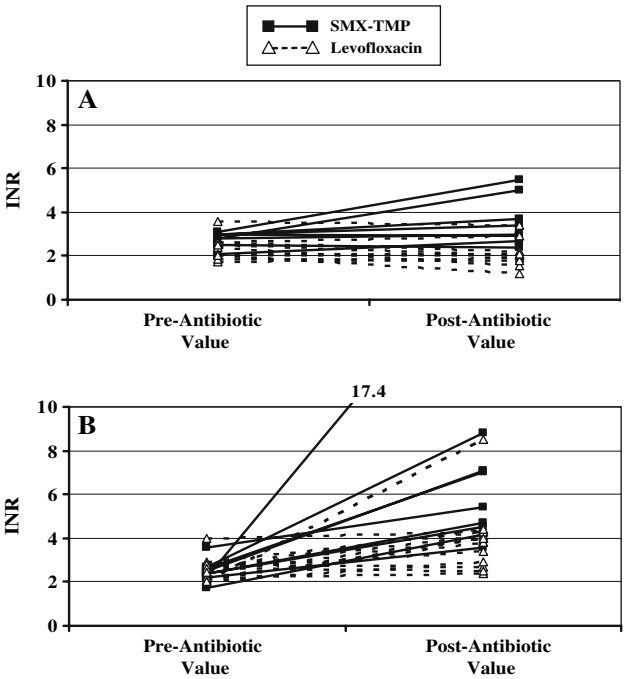

Fig. 2 INR results of each patient obtained before and after the initiation of antibiotic therapy. (**A**) Warfarin DR group. (**B**) Control group. Antibiotic legend applies to both panels. An off-scale post-antibiotic INR value (17.4) is shown in panel **B**

four levofloxacin-treated patients who had sub-therapeutic INR values after warfarin DR, two had slightly subtherapeutic INR values before starting antibiotic therapy (1.7, 1.83). The post-antibiotic INR values of these two patients were 1.9 and 1.8, respectively.

With respect to clinical outcomes, 2 patients (11%) in the DR group required transient interruption of warfarin dosing because the post-antibiotic INR result was supra-therapeutic (Table 2). In contrast, 12 patients within the control group (55%; 7 treated with TMP-SMX, 5 treated with levofloxacin) required transient warfarin dose interruption because of a supra-therapeutic post-antibiotic INR result ($P = 0.007$ vs. DR group). Within the warfarin DR group, no patients required vitamin K or blood product therapy, and there were no bleeding complications. Within the control group, 3 patients (14%; 2 treated with TMP-SMX, 1 treated with levofloxacin) were treated with oral vitamin K to correct excessive anticoagulation, and 1 patient (5%), who was treated with TMP-SMX, was transfused with fresh frozen plasma. No thrombotic complications were noted in either group.

Discussion

Our study compared two strategies for managing the chronically anticoagulated patient upon initiation of either

Table 2 Comparison of clinical outcomes for each treatment group

Clinical outcome	Dose reduction group ($n = 18$)	Control group ($n = 22$)	*P*-value
Interruption of warfarin dosing due to prolonged INR.	2 (11)	12 (55)	0.007
Administration of vitamin K	0 (0)	3 (14)	0.24
Administration of fresh frozen plasma	0 (0)	1 (5)	1.0

Numbers in parentheses represent % of total patients for each group

TMP-SMX or levofloxacin—i.e. preemptive warfarin DR vs. no change in warfarin dosing, with short-term follow-up of the INR being obtained for both strategies. Our data suggest that a preemptive warfarin DR of approximately 15% of the mean daily dose is effective in preventing INR prolongation compared to an expectant strategy, particularly for patients receiving TMP-SMX. In the group of patients receiving TMP-SMX, warfarin DR was associated with a significantly lower increase in INR values, as compared to control group patients. Nevertheless, 25% of TMP-SMX-treated patients in the DR group developed in INR >4.0, suggesting that even greater reductions in warfarin dose than those employed in our study are necessary in some patients to maintain therapeutic or near-therapeutic anticoagulation levels after starting TMP-SMX. However, it is possible that a % warfarin DR large enough to prevent INR prolongation to >4.0 in all or nearly all patients will lead to sub-therapeutic INR values in some patients. Therefore, we consider the % DR employed in our TMP-SMX-treated patients (mean 16%) as effective, since it resulted in maintaining an INR of <4.0 in 75% of patients, and an INR of <6.0 (a value used to define excessive anticoagulation in a major study of warfarin–antibiotic interactions [7]) in all patients. In contrast, the preemptive warfarin DR strategy appeared to be less beneficial in patients receiving levofloxacin, since the increase in INR with expectant management was mild, and some levofloxacin-treated patients with borderline-low pre-antibiotic INR values who were managed with a preemptive warfarin DR had sub-therapeutic INR values after initiating antibiotic therapy. These results are consistent with published studies in which the rise in INR was mild or non-existent when levofloxacin and warfarin were co-administered [10, 12]. Therefore, our data suggest that a preemptive warfarin DR may be highly effective for patients initiating TMP-SMX, but unnecessary for those initiating therapy with levofloxacin. While being the first study to demonstrate that prophylactic warfarin DR can effectively prevent excessive INR prolongation while avoiding subtherapeutic INRs in patients started on TMP-SMX, our study has limitations. The number of patients was small, which prevented comparison of the two treatment strategies in terms of hard bleeding and thrombotic events, and which probably prevented our study from achieving sufficient statistical power to adequately detect small, but potentially significant differences in the demographic composition of the two groups of patients we studied. Patients were not randomly assigned to the DR vs. control groups. Therefore, selection bias may have led to patients at higher risk of warfarin–antibiotic interaction being treated by preemptive warfarin DR, potentially overestimating the benefit of this management strategy in all warfarin/TMP-SMX-treated patients. A larger, prospective, randomized trial of preemptive warfarin DR vs. expectant strategy in patients initiating antibiotic therapy (not only with TMP-SMX and levofloxacin, but also with other antibiotics and short-term medications recognized to alter warfarin metabolism) would be of considerable interest. In addition to establishing which approach more effectively maintains therapeutic anticoagulation, such a trial would help to define the impact of preemptive warfarin DR on the frequency of INR testing, other cost-effectiveness endpoints, and patients' perceptions of short-term alterations in warfarin dosing.

In summary, our study suggests that a prophylactic, short-term, 10–20% warfarin DR can be a very effective strategy for maintaining a therapeutic level of anticoagulation in patients initiating treatment with TMP-SMX. While a prophylactic warfarin DR may be beneficial in some patients initiating levofloxacin therapy, an expectant strategy consisting of no change in the warfarin dosing and follow-up testing of the INR in approximately 5 days appears reasonable in these patients, since the degree of INR prolongation was mild or non-existent in the vast majority of patients, and a preemptive warfarin DR resulted in a fall in the level of anticoagulation to below the therapeutic range in some patients. Our study provides previously lacking data that complements expert opinion about preemptive warfarin DR in patients initiating antibiotic therapy, and should prove useful to clinicians facing this common clinical scenario.

Acknowledgements We thank the staff nurses of the University of Michigan Anticoagulation Service for their assistance in performing this study, and Judith Boura, M.S., William Beaumont Hospital, and John Hewett, Ph.D., University of Missouri-Columbia, for statistical analyses. Dr. Fay was a faculty member at the University of Michigan when this study was initiated, but had transitioned to the University of Missouri by the time of manuscript submission.

References

1. Hirsh J, Fuster V, Ansell J, Halperin JL (2003) American Heart Association/American College of Cardiology Foundation guide to warfarin therapy. J Am Coll Cardiol 41:1633–1652
2. Horton JD, Bushwick BM (1999) Warfarin therapy: evolving strategies in anticoagulation. Am Fam Phys 59:635–646
3. Whitlon DS, Sadowski JA, Suttie JW (1978) Mechanisms of coumarin action: significance of vitamin K epoxide reductase inhibition. Biochemistry 17:1371–1377
4. Breckenridge A (1978) Oral anticoagulant drugs: pharmacokinetic aspects. Semin Hematol 15:19–26
5. O'Reilly RA (1976) Vitamin K and the oral anticoagulant drugs. Annu Rev Med 27:245–261
6. Kelly JG, O'Malley K (1979) Clinical pharmacokinetics of oral anticoagulants. Clin Pharmacokinet 4:1–15
7. Visser LE, Penning-van Bees FJ (2002) Overanticoagulation associated with combined use of antibacterial drugs and acenocoumarol or phenprocoumon anticoagulants. Thromb Haemost 88:705–710
8. Baglin T (2002) Avoiding overanticoagulation: knowing your antibiotic. Thromb Haemost 88:703–704
9. Glasheen JJ, Fugit RV, Prochazka AV (2005) The risk of overanticoagulation with antibiotic use in outpatients on stable warfarin regimens. J Gen Intern Med 20:653–656
10. McCall KL, Scott JC, Anderson HG (2005) Retrospective evaluation of a possible interaction between warfarin and levofloxacin. Pharmacotherapy 25:67–73
11. Glasheen JJ, Fugit RV, Prochazka AV (2003) Effect of levofloxacin coadministration on the international normalized ratios during warfarin therapy. Pharmacotherapy 23:1079–1080, discussion 1080
12. Yamreudeewong W, Lower DL, Kilpatrick DM, Enlow AM, Burrows MM, Greenwood MC (2003) Effect of levofloxacin coadministration on the international normalized ratios during warfarin therapy. Pharmacotherapy 23:333–338
13. Jones CB, Fugate SE (2002) Levofloxacin and warfarin interaction. Ann Pharmacother 36:1554–1557
14. Gheno G, Cinetto L (2001) Levofloxacin-warfarin interaction. Eur J Clin Pharmacol 57:427
15. Ravnan SL, Locke C (2001) Levofloxacin and warfarin interaction. Pharmacotherapy 21:884–885