Thrombosis Research 130 (2012) 152–156

Contents lists available at SciVerse ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Regular Article

A Randomized Controlled Trial of Empiric Warfarin Dose Reduction with the Initiation of Doxycycline Therapy

Mary Beth Dowd, Kellie A. Kippes *, Daniel M. Witt, Thomas Delate, Kerri Martinez

Kaiser Permanente, Aurora, CO.

ARTICLE INFO

Article history:
Received 9 September 2011
Received in revised form 28 November 2011
Accepted 6 December 2011
Available online 4 January 2012

Keywords:
Drug interactions
pharmacists
doxycycline
warfarin

ABSTRACT

Background: When interacting medications, such as doxycycline, are initiated during warfarin therapy, one method to correct for non-therapeutic international normalized ratio (INR) is adjusting the warfarin dose, if necessary. Another approach is preemptive warfarin dose adjustment. This study's objective was to evaluate the utility of preemptive warfarin dose adjustment for preventing non-therapeutic INR following doxycycline-warfarin co-administration.

Methods: Patients were randomized to either a 10% to 20% preemptive warfarin dose reduction (intervention) or reactive warfarin dose adjustment (control) within 72 hours of warfarin-doxycycline co-administration. Subjects received a follow-up INR within 7 days (index INR). Primary outcome was the occurrence of index INR ≥ 1 point over the INR goal range upper limit. Secondary outcomes included INR control, purchases of prescription vitamin K, and warfarin-associated adverse events in the 30 days after doxycycline initiation.

Results: Twenty and 17 patients comprised the intervention and control groups. The intervention group's warfarin dose was reduced by a median of 11%. More control patients (n = 2) experienced an INR ≥ 1 point over the INR goal range upper limit compared to intervention (n = 0); however, the difference (12% vs. 0%) was not statistically significant (p = 0.20). A higher percentage of intervention patients had subtherapeutic index INRs compared to control (35% vs. 6%, p < 0.05). One patient from each group experienced warfarin-associated bleeding. No thromboembolic complications or vitamin K use were observed.

Conclusions: For warfarin patients initiating doxycycline therapy, preemptive warfarin dose reduction did not result in supratherapeutic INRs but increased the likelihood of subtherapeutic INRs compared to INR monitoring with reactive warfarin dose adjustment.

Introduction

There is variability among the numerous agents that interact with warfarin in regard to the magnitude of effect on anticoagulant response. For example, the risk of over-anticoagulation manifested as an elevation of the international normalized ratio (INR) varies from negligible to substantial with different antibiotics [1]. Tetracycline antibiotics are frequently prescribed during warfarin therapy and several cases of over-anticoagulation have been reported when doxycycline was co-administered with warfarin [2–5]. Although the mechanism for this interaction is not well defined, warfarin protein binding displacement may possibly explain transient increases in INR response.

Doxycycline is approximately 80% to 90% protein bound while warfarin is 97% protein bound [6]. Competition between warfarin and doxycycline for protein binding sites may transiently increase the free fraction of warfarin and hence the INR [6]. Inhibition of the cytochrome P-450 system by doxycycline may also inhibit the metabolism of warfarin resulting in more sustained warfarin plasma level increases [5]. The highest risk of over-anticoagulation has been reported to occur within seven to ten days after initiation of doxycycline [2–5].

Two different approaches to managing potential drug interactions with warfarin have been explored [7–10]. The conventional strategy consists of increased INR monitoring frequency with reactive warfarin dose adjustments based on INR value. The alternative strategy includes a preemptive warfarin dose reduction upon initiation of the interacting medication in anticipation of an elevated INR in addition to increased INR monitoring frequency [11,12].

In 2008, Ahmed and colleagues investigated the impact of reactive versus preemptive warfarin dose adjustment with the co-administration of warfarin and trimethoprim-sulfamethoxazole (TMP-SMX) or levofloxacin [11]. The results demonstrated that a preemptive warfarin dose reduction of 10% to 20% was effective in maintaining therapeutic anticoagulation with the co-administration of TMP-SMX. Conversely, preemptive warfarin dose reduction resulted in subtherapeutic INRs in 40% of patients during co-administration of levofloxacin [11]. It has been demonstrated in patients co-administered prednisone and

Abbreviations: INR, International normalized ratio; TMP-SMX, trimethoprim-sulfamethoxazole; KPCO, Kaiser Permanente Colorado; CPAAS, Clinical Pharmacy Anticoagulation and Anemia Service; IQR, Interquartile range.

* Corresponding author at: Kaiser Permanente, Exempla St. Joseph Hospital, 1835 Franklin St., Palliative Care Department: 5th floor, Denver, Colorado 80218. Tel.: +1 303 594 7929.
E-mail address: kellie.a.kippes@kp.org (K.A. Kippes).

0049-3848/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.thromres.2011.12.017

warfarin that preemptive warfarin dose reduction increased the likelihood of subtherapeutic follow up INRs but did not significantly reduce the risk of excessive anticoagulation [12]. These findings indicate that preemptive warfarin dose reduction may be an effective strategy for managing drug interactions that increase warfarin's anticoagulant effect in some but not all cases.

With limited information on the most effective approach to managing doxycycline co-administration with warfarin, it is prudent to further investigate management strategies. Thus, the purpose of this study was to assess the effectiveness and safety of preemptive warfarin dose reduction compared to reactive warfarin dose adjustment in a randomized controlled trial among patients receiving co-administration of warfarin and doxycycline.

Materials and methods

Study design

This was a randomized controlled trial. All patients provided informed consent prior to randomization. Patients on chronic warfarin therapy who purchased a doxycycline prescription were randomly assigned to receive either a one-time 10% to 20% preemptive warfarin dose reduction (intervention group) or reactive warfarin dose adjustment (control group) with follow-up INR monitoring. Data were collected from integrated electronic medical, pharmacy, laboratory, and administrative record databases. The study was reviewed and approved by the Kaiser Permanente Colorado (KPCO) Institutional Review Board.

Setting

This study was conducted at KPCO, an integrated, not-for-profit healthcare delivery system that provides services to over 533,000 members in Colorado. Anticoagulation services at KPCO are provided by the centralized Clinical Pharmacy Anticoagulation and Anemia Service (CPAAS) [13]. Working collaboratively with referring physicians and using standardized dosing algorithms, CPAAS clinical pharmacists initiate, adjust and refill anticoagulant medications and order relevant laboratory tests. Laboratory measures for INRs are performed at KPCO's central hematology laboratory.

Study population

Study inclusion criteria were: 1) ≥18 years of age at time of recruitment; 2) receiving warfarin therapy for at least 3 months prior to study enrollment; and 3) had purchased a prescription of doxycycline at KPCO. Study exclusion criteria included: 1) enrolled in another study; 2) receiving another prescription medication that may affect INR control in addition to doxycycline; or 3) pregnant at the time of recruitment.

Intervention

An electronically-generated, daily report of warfarin-receiving patients who had purchased a warfarin-interacting medication was used to identify patient's prescribed doxycycline between January 1 and June 30, 2009. Potential study participants were contacted via telephone within 72 hours of doxycycline purchase and eligible patients were then invited to participate in the study. While the 72-hour time frame was chosen to allow recruitment of patients purchasing doxycycline during a weekend, most patients were contacted within 24 hours. Enrolled patients were randomized into the intervention or control groups using computer-generated random numbers. Baseline INRs were not drawn during the study but obtained during usual care prior to study enrollment; therefore, baseline INR values may have been from a blood draw that was performed up to 30 days prior to study enrollment. A subject's most proximal INR value recorded prior to study enrollment was used as his/her baseline INR.

Intervention subjects were instructed to reduce their weekly warfarin dose by 10% to 20% while control subjects continued their current warfarin dose. The majority of patients in the intervention group reduced their warfarin dose on the day they were enrolled in the study or within 48 hours depending on their last INR value. Both groups had a follow-up INR within 7 days of doxycycline initiation as per standard CPAAS management. At this and all follow-up visits, subjects were specifically asked about changes in diet or herbal medications that may have affected their INR result. The actual percent reduction in warfarin dose was determined by the clinical judgment of the enrolling pharmacist and the subject's current tablet strength of warfarin. Clinical factors considered included the subject's baseline INR, age, and historical INR responses to potential interacting medications.

Outcomes

The primary outcome was the occurrence of an index INR value ≥1 point over the upper limit of the subjects' therapeutic INR range within 7 days after doxycycline initiation (e.g., a subject with an INR goal of 2 to 3 would reach the primary outcome when his/her follow-up INR was ≥4). Secondary outcomes included the percentage of index INR values that were within, above, and below the subject's therapeutic range and absolute change from baseline to follow-up INR. In addition, percentage of follow-up INR values within, above, and below the subject's therapeutic range, purchases of prescription vitamin K, and warfarin-associated adverse events (bleeding and thromboembolism) in the 30 days after doxycycline initiation were assessed.

Data analysis

An estimated sample size of at least 20 subjects in each group was required to detect a reduction of 72% in rate of the primary outcome [8] in the intervention group compared to control group with 80% power and an alpha of 0.05. Continuous data were expressed as mean ± standard deviation or median with interquartile range and compared using independent sample *t*-test or Wilcoxon rank sum test, as appropriate. Categorical data were expressed as percentages and compared using the chi-square test of association or Fisher's Exact test, as appropriate. All analyses were performed using SAS 9.1 (SAS Institute, Cary, NC).

Results

Eligible participants were recruited from January through June 2009. A total of 39 subjects were randomized to either preemptive intervention (n = 21) or control (n = 18) groups, respectively. A total of 2 (1 intervention and 1 control) subjects failed to return for their follow-up INR (within 7 days of doxycycline initiation). Thus, 20 and 17 intervention and control patients, respectively, completed the study and were included in the analysis.

The groups were comparable in regards to age, gender, indication for warfarin therapy, and dosing (all $p > 0.05$) (Table 1). The intervention group had a median 11.1% (Interquartile range [IQR] = 10.0% to 12.5%) reduction in their weekly warfarin dose. While more control subjects (n = 2) had an index INR value ≥1 point over the INR goal range upper limit compared to intervention group subjects (n = 0), the difference (11.8% vs.0.0%) was not statistically significant ($p = 0.20$). The rate of index INR values below the target INR range was higher in the intervention group compared to the control group (35.0% vs. 5.9%, $p < 0.05$) (Fig. 1). Conversely, the between-group differences in percentages of index INR values above the target range (15.0% in the intervention group vs 35.3% in the control group.