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Preemptive dose reduction of warfarin in patients initiating metronidazole

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Abstract

Background: The goal of this study was to determine if preemptive dose reduction (PDR) of warfarin is effective in maintaining therapeutic anticoagulation in patients initiating metronidazole.

Methods: This is a retrospective, single-center, cohort study in a pharmacist-managed anticoagulation clinic of a university affiliated Veteran's Affairs (VA) Medical Center. Subjects were anticoagulation patients initiating metronidazole between 1 January 2002 and 30 March 2009. At the time of metronidazole initiation, patients were managed with PDR of warfarin or no dose reduction. The primary outcome was the average change in International Normalized Ratio (INR) between patients that received PDR vs. those that did not.

Results: In total, 20 patients met inclusion criteria with seven patients receiving PDR at the time of initiation of metronidazole, whereas 13 did not. Patients managed with PDR and those that were not were similar in age (mean±SD 69.4±12.9 years vs. 72.1±9.9 years, p=0.61), mean baseline INR before metronidazole (2.58±0.49 vs. 2.57±0.66, p=0.98), and mean time to follow-up after initiation of metronidazole (5.6±2.9 days vs. 7.0±3.7 days, p=0.40), respectively. The primary outcome was statistically significant with a mean difference in INR of 1.28 (p=0.01) between patients managed with PDR vs. those that were not. The mean preemptive warfarin dose reduction was 34.6%±13.4% which resulted in no significant increase in INR (p=0.61). Secondary outcomes including INR values >4.0 (0% vs. 46%, p=0.05), the average number of warfarin doses omitted (0.43±0.79 vs. 1.15±1.27, p=0.17), use of phytonadione or fresh frozen plasma, and rates of bleeding events were not significantly different between groups. No thromboembolic events occurred during the 30 days following metronidazole therapy.

Conclusions: In patients determined to be appropriate candidates for PDR, a 30%–35% reduction in mean daily warfarin dose was effective in maintaining therapeutic anticoagulation in patients started on concomitant metronidazole.

Keywords: anticoagulation; drug interaction; metronidazole; warfarin.

Introduction

Warfarin remains the cornerstone of oral anticoagulation therapy despite the risk of serious hemorrhagic events and potential for clinically significant drug interactions (1–3). Antibiotics can be especially troublesome in patients receiving warfarin as they are prescribed intermittently and their use can alter the International Normalized Ratio (INR) from both pharmacokinetic and pharmacodynamic mechanisms (4).

In 1976, O'Reilly documented a drug interaction between warfarin and metronidazole (5). This interaction occurs as a result of enzyme inhibition of CYP 2C9, which is responsible for the metabolism of *S*-warfarin. This interaction can significantly increase the INR, as well as risk of hemorrhage (6–9). When initiating an antibiotic known to have a significant enzyme inhibition interaction with warfarin [e.g., metronidazole, fluconazole, trimethoprim-sulfamethoxazole (TMP-SMX)], it is necessary to remeasure the INR within the first few days of concomitant therapy. Some clinicians preemptively reduce the dose of warfarin up to 50% often based solely on anecdotal experience (10–12).

In warfarin-treated patients initiating TMP-SMX, Ahmed and colleagues demonstrated that a 10%–20% preemptive warfarin dose reduction was effective in maintaining therapeutic anticoagulation (13). The objective of this study was to determine if preemptive dose reduction (PDR) of warfarin could also be an effective strategy in anticoagulation patients prescribed metronidazole.

Materials and methods

We completed a retrospective study of a cohort of patients at an anticoagulation clinic of the university affiliated Veteran's Affairs (VA) Medical Center located in Iowa City, IA, USA. This clinic utilizes clinical pharmacists to manage more than 1200 patients in Eastern Iowa and the Western Illinois area. The University of Iowa Institutional Review Board and the VA Research and Development committee evaluated and approved the study. Owing to the minimal risks involved, informed consent was not deemed necessary.

The study population included patients 18 years or older who received outpatient monitoring for warfarin therapy between 1 January 2002 and 30 March 2009. Inclusion criteria included documentation that patients received concomitant metronidazole and

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warfarin. Patients must have received a consistent weekly warfarin dose for 2 weeks preceding metronidazole initiation. Finally, patients had to have a follow-up INR while receiving metronidazole or within 3 days of completing the course. Patients were excluded if there was documentation that the warfarin dose was modified within the previous 2 weeks, if metronidazole was discontinued prior to obtaining a follow-up INR, or if the patient started another medication known to have a significant interaction with warfarin.

Identification of anticoagulation patients who received metronidazole occurred in two ways. First, all anticoagulation patient encounters in this clinic are coded using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code V58.61 "Long term use of anticoagulants". This diagnosis code was linked to new prescriptions for metronidazole to generate a list of patients that received anticoagulation management and a prescription of metronidazole. Because this diagnosis code had only been utilized by this clinic for part of the defined study period, a manual review of anticoagulation clinic charts was also conducted. This paper record system continuously documents the current warfarin dose, INR, newly started medications, and other factors that could affect the INR or risk of bleeding. The manual review ensured that patients meeting inclusion criteria were not overlooked as this allowed researchers to identify patients who received warfarin through the VA but received metronidazole from healthcare providers outside the VA healthcare system.

The primary endpoint was the average change in INR between patients who were managed with PDR of warfarin vs. those that were not at the time of metronidazole initiation. Secondary endpoints included incidence of follow-up INR values ≥4.0, the average number of warfarin doses omitted, and use of phytonadione or fresh frozen plasma. Finally, major and minor bleeding as well as thromboembolic events were recorded in the 30 days after the course of metronidazole was completed.

Baseline between-group comparisons for categorical variables were performed using the χ^2 or Fisher exact test where appropriate. Continuous baseline variables were compared using the Student t-test for normally distributed variables and the Mann-Whitney U-test for non-parametric variables. The primary outcome analysis utilized the Student t-test. All comparisons are reported as mean±SD. A paired-sample t-test was used for within-group secondary analysis. The χ^2, Fisher exact or Student t-test was used for between-group secondary analyses. All tests were two-tailed and a p-value <0.05 was predetermined to represent statistical significance. All analyses were performed with SPSS, version 15.0 (SPSS Inc., Chicago, IL, USA).

Results

Of 1162 anticoagulation patients in our study population, we identified 79 patients who received concurrent metronidazole. A total of 20 patients met inclusion criteria; seven patients were managed with PDR, and 13 were not (Figure 1).

The study population was 100% male and patients in both groups were similar in age, anticoagulation diagnosis, warfarin dose (mg/week), baseline INR, and the percentage within their respective target INR range prior to initiating metronidazole (Table 1). The average daily dose of metronidazole was comparable between patients managed with PDR vs. those that were not (1500 mg/day vs. 1475 mg/day, respectively, p=0.91), as was the mean time to follow-up (5.6±2.9 days vs. 7.0±3.7 days, p=0.40).

Patients managed with PDR had a mean warfarin reduction of 34.6%±13.4% and these patients did not demonstrate a significant increase in INR after initiating metronidazole (0.19±0.92, p=0.61). Patients that were not managed with PDR experienced a significant increase in the INR after initiation of metronidazole of 1.47±0.97 (p=0.001). The primary endpoint, the average difference in INR between groups was significant at 1.28 (p=0.01) (Figure 2). Figure 3 highlights individual INR results in patients managed with PDR of warfarin compared to those not receiving PDR.

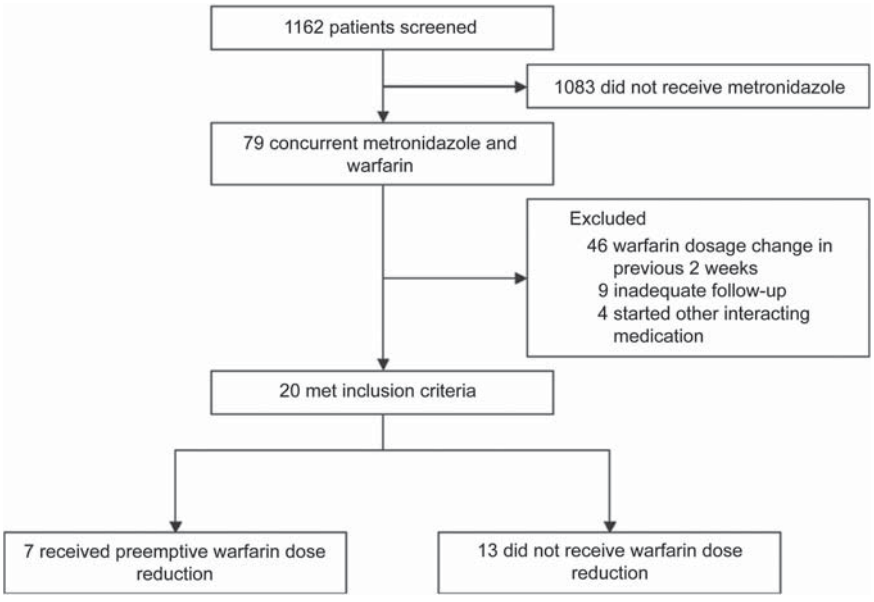

Figure 1 Flow diagram of patient identification.

Table 1 Baseline characteristics of study patients.

Characteristic	No. (%) of patients		p-Value
	Dose-reduced (n=7)	Control (n=13)	
Demographics			
Male	7 (100.0)	13 (100.0)	1.0
Age, mean±SD (years)	69.4±12.9	72.1±9.9	0.61
Warfarin dose, mean±SD, mg/week	36.6±15.9	34.5±12.9	0.70
Target INR range			
2.0–3.0	6 (85.7)	11 (84.6)	1.0
Other	1 (14.3)	2 (15.4)	1.0
Baseline INR, mean±SD	2.58±0.49	2.57±0.66	0.90
Within target INR range	6 (85.7)	11 (84.6)	1.0
Anticoagulation diagnosis			
Atrial fibrillation	4 (57.1)	9 (69.2)	0.65
DVT	1 (14.3)	2 (15.4)	1.0
Prosthetic valve	1 (14.3)	1 (7.7)	1.0
Other	1 (14.3)	1 (7.7)	1.0

INR, International Normalized Ratio; DVT, deep vein thrombosis.

Two patients (29%) managed with PDR of warfarin required temporary interruption of warfarin for a supratherapeutic INR compared to eight patients (62%) that were not managed with PDR. Six of these eight supratherapeutic INR values were ≥4.0, whereas none of the patients managed with PDR had an INR >4.0 at follow-up (p=0.05). No patient in either group required phytonadione or blood products nor did any thromboembolic events occur. Two patients, both of whom were not managed with PDR, developed minor bleeding complications (p=0.52; Table 2).

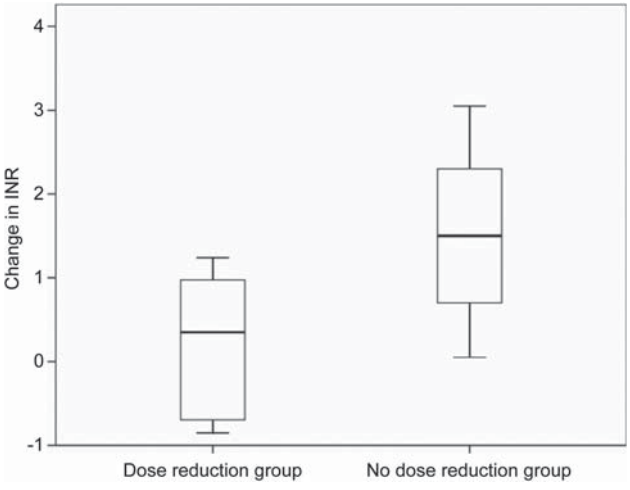

Figure 2 Change in INR from baseline after initiation of metronidazole.

Mean change in INR between patients managed with preemptive warfarin dose reduction and no dose reduction. There was a significant increase in INR among patients who did not receive preemptive dose reduction (p=0.001) and a non-significant increase in INR in patients managed with preemptive dose reduction.

Discussion

Although the interaction between warfarin and metronidazole has been documented for over 30 years, to the authors' knowledge, this is the first study examining the effects of PDR of warfarin in patients receiving concomitant metronidazole. We observed a significant change in INR among patients not managed with warfarin dose reduction at the time of metronidazole initiation. The increase in INR is likely to be clinically important as the risk for intracranial hemorrhage doubles for each 1.0 increase in INR and increases as the INR exceeds 4.0 (14–17). It has also been documented that concomitant metronidazole and warfarin is associated with an increased risk of hemorrhage (7, 8).

Although no difference in secondary endpoints was observed, there was a consistent trend towards significance. Most notably, 46% of patients not managed with PDR developed an INR >4.0 and these patients required more omitted doses. Also, two patients not managed with PDR had minor bleeding complications: a nosebleed requiring an emergency room visit and development of bruising side effects in another patient. A subtherapeutic INR occurred in two patients managed with PDR – a non-significant number compared to patients not managed with PDR. Of note, both patients were at the bottom tertile of their INR range before initiation of metronidazole. The INR of one patient decreased to 1.2 on follow-up, and in this patient, the warfarin dose was preemptively reduced by 62%, which is more than the average dose reduction of all other patients. As the magnitude of PDR and this patient's subsequent INR response was an outlier, a re-analyses for the primary endpoint was completed with this patient removed. Results of the primary endpoint remained significant (p=0.03). Without the outlier average percent reduction in warfarin dose decreased to 30%±6.7%. These results suggest that a 30%–35% PDR of warfarin is more effective in maintaining a therapeutic INR compared to no dose reduction in patients started on metronidazole. No patient managed with PDR developed an INR >4.0 indicating that dose reductions >40% are most probably unnecessary.

Our study does not suggest a 30%–35% warfarin dose reduction is appropriate for all patients, as this simply represented the average dose reduction that patients received. In fact, for patients determined to be at high risk for thromboembolic events it might be appropriate to not reduce the warfarin dose and simply repeat an INR no later than 72 h after initiation of the combination. The risk of a subtherapeutic INR secondary to PDR, and ultimately increasing risk of thromboembolic events, should be weighed against risk of bleeding. There were no documented thromboembolic events 30 days following completion of metronidazole.

There are limitations to our study, most notably the retrospective design and small study numbers. The study lacked adequate power to assess secondary endpoints. In addition, patients were not randomly allocated to treatment groups which might have resulted in selection bias as certain patients could have had their dose reduced based on individualized risk factors. Finally, many other factors alter the INR includ-

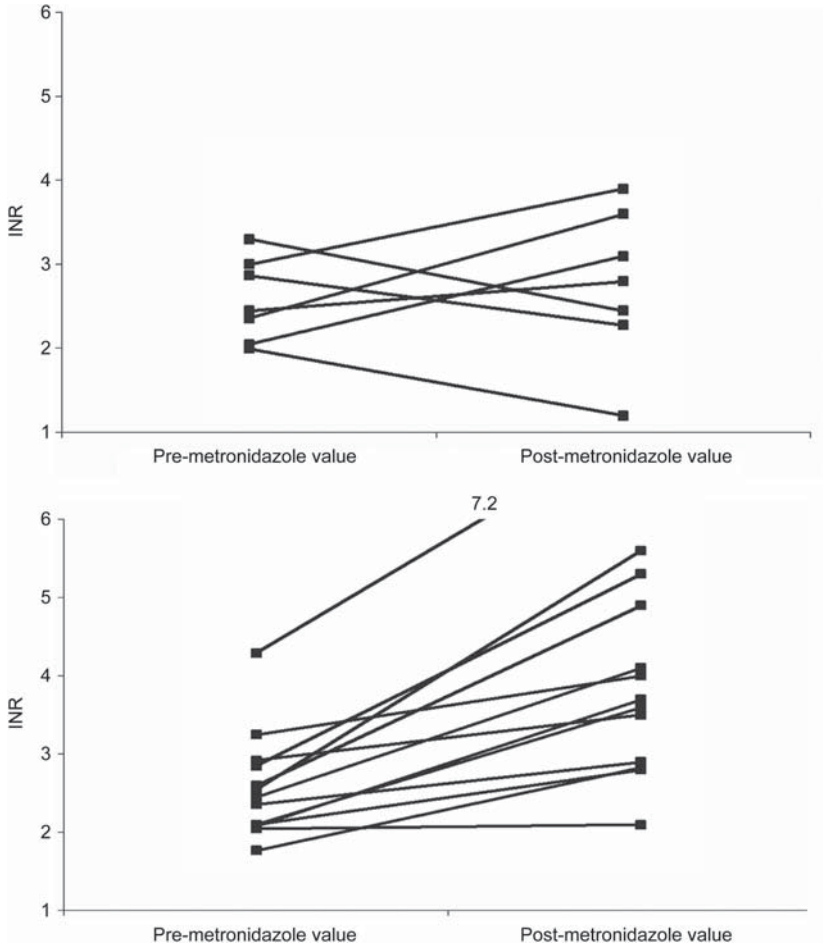

Figure 3 Individual INR results between groups.
Individual INR results before and after initiation of metronidazole in patients with preemptive warfarin dose reduction (top) or no preemptive dose reduction (bottom). An off-scale post-metronidazole INR value of 7.2 is shown in the bottom panel.

Table 2 INR classification and outcomes following initiation of metronidazole.

Measure	No. (%) of patients		p-Value
	Dose-reduced (n=7)	No dose reduction (n=13)	
Subtherapeutic INR	2 (28.6)	0 (0.0)	0.11
Supratherapeutic INR	3 (42.9)	9 (69.2)	0.36
INR >4.0	0 (0.0)	6 (46.2)	0.05
Omitted doses, mean±SD	0.43±0.79	1.15±1.21	0.17
Minor hemorrhagic events[a]	0 (0.0)	2 (15.4)	0.52

[a]Minor hemorrhagic events included all other bleeding events not meeting criteria for a major bleed. Major hemorrhagic events included fatal or life-threatening bleeding events, evidence of intracranial or retroperitoneal bleeding or any bleeding event that required hospitalization or transfusion. INR, International Normalized Ratio.

ing changes in dietary vitamin K, acute changes in health, and consumption of alcohol. Our study did not account for all factors that can routinely change the INR. However, prior to initiation of metronidazole patients in both groups were similar in age, gender, anticoagulation diagnosis, target INR, and mean warfarin dose. Patients in both groups had similar mean INR values and had received no recent changes in their warfarin dose. Moreover, patients in both groups were treated with similar daily doses of metronidazole suggesting that dose-response was not a factor. Finally, time to INR follow-up was similar between groups and coincided with peak of the metronidazole-warfarin interaction suggesting that most patient INR measurements were at or near their peak (6).

Conclusions

The study findings suggest a 30%–35% PDR of warfarin in mean daily warfarin dose can effectively maintain a therapeutic INR in warfarin managed patients started on metronidazole. For practitioners facing this clinical dilemma, our study results provide guidance to appropriately manage this well-documented interaction. A larger, prospective, randomized study of PDR of warfarin would be helpful in expanding on these data.

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Conflict of interest statement

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