Evaluation of the Conversion of the Brand Equivalent of Warfarin to Its Generic

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Anticoagulation therapy with warfarin or its brand equivalent is a great concern of health care providers at the G.V. (Sonny) Montgomery VAMC because of its possible adverse effects on patients. Switching patients from the brand to the generic may be cost-effective, but does it put the patient at an even greater risk?

Warfarin, a vitamin-K antagonist, exerts its anticoagulant effects by inhibiting the production of vitamin K-dependent clotting factors.[1] Warfarin is monitored by the international normalized ratio (INR), a standardized measure of prothrombin time, which is used to determine the clotting tendency of the blood.[2] Warfarin is a high-risk medication due to its narrow therapeutic index. Subtherapeutic levels increase the risk of thromboembolism while supratherapeutic levels increase the risk of hemorrhage. The metabolism of warfarin is affected by various prescription, over-the-counter, and botanical medications, food, genetic variations, and diseases.[1]

The FDA has approved many generic warfarin formulations due to proven bioequivalence to the reference formulation. However, clinicians remain hesitant to switch between the brand and its generics since warfarin is a high-risk medication. It is the VHA policy that each facility has a defined anticoagulation management program to individualize patient care and reduce the likelihood of patient harm.[2] Further, the Joint Commission National Patient Safety Goal 03.05.01 was created to "reduce the likelihood of patient harm associated with the use of anticoagulant therapy."[3]

The Pharmacy Benefits Manager removed the brand warfarin from the "Do Not Substitute" list, allowing generic manufacturers to place contracting bids for the use of their product in the VA and DoD. The brand warfarin remained under contract but at a higher price; thus, the decision was made to convert to Golden State Medical Supply, a distributor of warfarin through Taro Pharmaceutical Industries Ltd, as the new formulary agent at about a 95% cost savings.

Several articles have been published on the conversion between the brand warfarin and its generic in various ambulatory care settings. In these studies, conflicting results exist about whether conversion between the brand warfarin and its generics produce clinically significant changes in INR.[4-8] Conflicting results increase clinician hesitance to make the conversion to the generic warfarin despite medication cost savings. Also, since the INR of patients tends to fluctuate above or below the desired INR range, addition of another variable is of concern to many health care providers. Due to these concerns, conversion at the G.V. (Sonny) Montgomery VAMC in Montgomery, Mississippi, was implemented in the pharmacist-managed Primary Care Coagulation Clinics. In an attempt to validate or alleviate these concerns from providers, the authors opted to evaluate the effect of conversion from brand warfarin to Taro's generic warfarin. The primary purpose of this study was to quantify the change in INR stability by evaluating the mean INR and percentage of patients within their target INR range before and after conversion. The second purpose of the study was to evaluate the effect conversion had on safety.

METHODS

This retrospective chart review was approved by the VA Institutional Review Board and Research and Development Committee. Inclusion criteria were all outpatients receiving brand warfarin for any labeled indication at the G.V. (Sonny) Montgomery VAMC on February 1, 2010, converted to generic warfarin during the data collection period and followed by a pharmacist in a Primary Care Coagulation Clinic. Exclusion criteria were veterans with a history of noncompliance, reported nonconversion to generic warfarin, and fewer than 3 INR values before and after conversion within the data collection period. Therefore, the 3 INRs obtained before and after conversion could have been done within 3 weeks to 3 months of each other, depending on patient factors and provider preference. Data were collected through September

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20, 2010. Initially, 556 patients who had active brand warfarin prescriptions as of February 1, 2010, were screened. After exclusion criteria, the study population was 104 patients with 3 INRs before and after conversion; thus totaling 312 pre- and postconversion INRs. The majority of patients were excluded due to the absence of 3 INRs before and after conversion or missing or taking extra doses for any reason other than the pharmacists' instruction.

The data in Table 1 were collected retrospectively using the Computerized Patient Record System: age, sex, indication for warfarin, patient-specific INR range, 3 INR laboratory values before and after conversion, and patient-reported adverse events (AEs). Population demographics are also reported in Table 1.

Table 1. Retrospective data collected using the Computerized Patient Record System

n = 104	
Age in years (mean [SD])	69 (10)
Sex	(%)
Male	99
Female	1
Target INR range	(%)
2-3	86
2.5-3.5	11
Other	3
Indication(s)	(%)
Atrial fibrillation	51
Venous thromboembolism	30
Cerebrovascular accident	17
Prosthetic valve	11
Myocardial infarction	4
Other	26

INR = international normalized ratio.

RESULTS AND DISCUSSION

MVPstats, Version 9 (MVP Program, Vancouver, WA) and SPSS, Version 10 (SPSS, Inc., Chicago, IL) were the statistical software used for data analysis. A paired sample *t* test was used to compare mean INR values before and after conversion. Variability of INR values before and after conversion was analyzed by use of a test of heterogeneity of variance for non-independent samples. Separate Fisher exact tests were used to compare the proportion of INR values below, within, and above the desired INR range before and after conversion as well as the proportion of patients with AEs. An alpha level of 0.05 was used to determine statistical significance.

The mean INR before and after conversion was 2.54 and 2.61, respectively (P = .217) (Table 2). The test for heterogeneity of non-independent variances using the standard deviation resulted in +/- 0.396 and +/- 0.466 before and after conversion, respectively. The difference in variability before and after conversion is significant (P = .085) with greater variability noted after conversion.

Table 2. Mean INR before and after conversion

	INR mean		*P* value
	Before conversion	After conversion	
INR values	(n = 312)	(n = 312)	
INR	3	3	= .217
SD	+/- 0.396	+/- 0.466	= .085

INR = international normalized ratio.

There was not a significant difference in the proportion of INRs below or within the desired INR range before and after conversion (Table 3). However, there was a significantly greater proportion of supratherapeutic INR values after conversion (P = .025).

The proportion of patients who experienced an AE was not statistically significant (Table 4). Adverse events were counted as 1 per patient even if the patient experienced more than 1 AE. The most commonly reported AEs were epistaxis, ecchymosis, gingival bleeding, hematuria, and rectal bleeding.

LIMITATIONS

This study is limited, because it is a retrospective study; investigators were not able to control for confounding factors, such as change in

Table 3. Proportion of INRs below or within the desired INR range before and after conversion

	Percentage of INRs		*P* value
	Before conversion	After conversion	
INR values	(n = 312)	(n = 312)	
Below desired INR range	16	16	NS
Within desired INR range	72	66	= .100
Above desired INR range	12	19	= .025

INR = international normalized ratio; NS = not significant.

Table 4. Percentage of patients who experienced an AE before and after conversion

(n = 104)		*P* value
Before conversion	After conversion	
8	7	NS

AE = adverse event; NS = not significant.

diet or medications. Brand warfarin management is more an art than a science due to many patient-specific factors; dose adjustments and returns to the clinic for INR monitoring were all provider-specific. There was no power analysis; therefore, the investigators were unable to determine whether the sample size was adequate. Also, not all patients began warfarin on the pharmacy-fill date. Some notes specified the exact start date, because the patients were instructed to complete their brand warfarin supply before starting the generic. Patients had to complete the entire study period to be included in data collection. This constraint resulted in the exclusion of patients who had warfarin-related AEs. Last, these results apply only to conversions between brand warfarin and the specified generic, because other generics of warfarin were not used in the study.

CONCLUSION

The study failed to find a correlation between conversion from brand warfarin to generic warfarin on therapeutic INRs. Although a correlation with conversion and supratherapeutic INRs was found, this finding is not clinically significant, since safety was not affected as evidenced by an insignificant change in AEs. Future analysis is necessary to identify specific subgroups that may be adversely affected. Given the close monitoring the warfarin patients at the G.V. (Sonny) Montgomery VAMC receive, the conversion from brand to generic warfarin at the facility continued without any major events reported with study patients. ●

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