Unexpected FVII Levels When Monitoring Coumadin Patients with Unstable INRs

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Introduction

The International Normalized ratio (INR) has been widely touted in the monitoring of oral anticoagulant treatment. In spite of problems, adoption of the INR system has contributed to reducing the number of over anticoagulated patients and fostering confidence in long-term oral anticoagulant therapy (OAT).[1]

However, problems have occurred with some investigators and clinicians when monitoring subjects with the presence of a lupus anticoagulant (LA). The recommended therapeutic range of INR for OAT patients with the presence of a LA is controversial (INR: 2.5 to 3.5).[2] It has been suggested that using the INR to monitor these patients may be inadequate due to interference by the presence of a LA on the clot-based prothrombin time (PT) assay.[3] Some investigators have suggested using the prothrombin-proconvertin assay in lieu of the PT/INR for patients with this disorder since it doesn't appear to be affected by a LA's inhibitory actions.[4-6]. Others have suggested monitoring by measuring coagulation factors II and X by either chromogenic or one-stage clotting assays based on at least three dilutions to lessen the LA inhibitor effect [3,7,8]. However, Robert in a study using the STA mechanical endpoint coagulation system, found little effect of the presence of a LA on PT/INR results using different thromboplastins.[9]. One small exception was a subgroup of six patients in which a recombinant thromboplastin (Innovin, Dade-Behring) was used.

In our patient population, we have a group of subjects who have unstable INR values that require frequent coagulation testing and adjustment of medication doses. These subjects have a variety of hypercoaguable disorders and clinical problems (antiphospholipid antibody syndrome and related disorders, protein C and S deficiency, antithrombin III deficiency, and some thrombotic states not yet identified).

The initial purpose of our study was to evaluate the feasibility of using chromogenic factor assays for monitoring oral anticoagulant therapy (OAT) patients with unstable INR values with and without the presence of a coagulation inhibitor instead of utilizing the Prothrombin (PT) derived INR result. What we encountered were unexpected levels of FVII in both the clottable and chromogenic assays.

Materials and Methods

We monitored nineteen OAT subjects with hypercoaguable states who required weekly or biweekly INR checks and subsequent adjustments in their coumadin dosing. All of the subjects had been on OAT therapy for at least 8 weeks. Each subject was monitored for at least 6 time points over a period of approximately one to two months. The PT/INR results were obtained using two different reagent/instrument combinations on citrated platelet-poor plasma (MLA 1600 [Hemoliance], Thromboplastin-DS, ISI 1.21 (Pacific-Hemostasis), STA (Diagnostica Stago), Neoplastine CI+, ISI 1.14 (Diagnostica-Stago). The ISI values were obtained by local on-site calibration of each reagent/instrument system. Chromogenic assays for FVII (Diapharma) were performed by a validated in-house microtiter method and chromogenic FX (Diapharma) tests were performed by validated in-house method on the MLA 900C (Hemoliance). Clottable FII, FVII and FX assays were performed on the STA using Neoplastine CI+.

As a control we performed PT/INR's, clottable FII, FVII and FX levels on 50 individuals with INR values that had been stable over 3 time points. We then surveyed 30 of these individuals with stable INR's to rule out the possibility of cold activation of FVII using the STA reagent/ instrument combination. We assayed fresh specimens and the same samples stored at -70°C for 48 hours and then rapidly thawed at 37°C.

Results

Table 1: Unstable INR subjects (19 patients with a minimum of 6 of each assay).

N=19	Mean INR (n=163)	Mean FII: Clottable	Mean FVII: Clottable	Mean FX Clottable	Mean FVII Chromo	Mean FX Chromo
STA	2.26	29.5%	52.9%	22%		
MLA 1600	2.73					
MLA 900C						33.2%
Microtiter					62.7%	
>40% activity			62.6%		83.2%	

Table 2: Stable INR subjects (50 subjects with stable INR over 3 time points).

(N=50)	Mean INR	Mean FII Clottable	Mean FVII Clottable	Mean FX Clottable
STA	3.57	21.7%	34.5%	13.4%

Table 3: Stable INR subjects (30 subjects with stable INR for FVII Cold Activation).

STA	Mean INR	Mean FVII: Clottable
Fresh specimens	3.34	37.5%
Frozen specimens	3.64	33.5%

Discussion

Our physicians in the coumadin clinic want Vitamin K dependent coagulation factor (FII, FVII, and FX) values in the OAT subjects to be approximately 30.0% or less. The mean INR values were in the therapeutic range for all patients (2.0-3.5) not just LA subjects (2.5-3.5) or slightly higher. We were surprised at the number of results of the clottable (62.6%) and chromogenic (83.2%) FVII assays in the unstable INR subjects that were >40.0% activity. This value is considered within normal limits on patients who are not receiving OAT treatment.[10] Patients with stable INR values, had higher INR's, and the FVII levels were clinically lower. There was no evidence of cold activation elevation of the FVII levels in our setting.

Our study showed that our patients, with unstable INR values, might be in the INR therapeutic range but the FVII levels are higher than is desired in OAT subjects. These unexpected results may give us an insight into the reason for these individuals unstable INR occurrences.

Further studies to look at clinical outcomes of these unstable INR patients are currently ongoing.

References

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