

Letter to the Editor

More on the Limitations of the Activated Partial Thromboplastin Time for Monitoring Argatroban Therapy

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We read with interest the recent article on laboratory monitoring of parental direct thrombin inhibitors by Van Cott et al.¹ This is a welcome addition to the literature assisting laboratories in a difficult area. We agree that the activated partial thromboplastin time (aPTT) assay is the most commonly used method for monitoring patients on argatroban. We would like the opportunity to offer additional considerations on the use of aPTT, including its limitations, and the advantages of using the less common methods of drug calibrated specific assays.

The cited target range of 1.5 to 3 × baseline aPTT ratio not exceeding 100s, from the Summary of Product Characteristics (SmPC) addressing the use for argatroban, is partly based on an early trial² that permitted inclusion of patients with a baseline aPTT ratio of up to 2 (i.e., with gross prolongation of aPTT in advance of any argatroban infusion); thus, some cases might have been within the assigned target range for therapy before any drug was even administered. This could be caused by the underlying condition of the patient with associated coagulopathy. This is an obvious limitation of use of aPTT for monitoring. The authors of the recent article in this journal¹ acknowledge that monitoring of argatroban using aPTT alone is difficult or impossible if the patient has a prolonged aPTT at baseline (e.g., caused by lupus anticoagulants or deficiencies in factors VIII, IX, XI, or XII).

There is a good deal of additional literature evidence identifying the potential problems of using the aPTT as the only test to monitor argatroban. Curvers et al³ suggest that this will lead to overestimation of the drug concentration. Furthermore, as mentioned by Van Cott and coworkers,¹ aPTT has been shown to have some plateau effect with argatroban, and Keyl et al⁴ showed that in critically ill patients, this plateau occurred at 72 seconds (determined using Pathromtin SL) and equivalent to a drug concentration

of 0.85 µg/mL. In the original trial,⁵ aPTT using Actin FSL also showed a plateau effect, which occurred at 1 µg/mL. Underestimation of drug concentration and argatroban “resistance” has also been demonstrated in elevated levels of factor VIII.⁶ Plasma in patients with liver disease spiked with argatroban demonstrated that they would receive lower doses of argatroban than those without liver disease, if using the aPTT to monitor.⁷ Wanat et al⁸ have demonstrated in a patient that the dilute thrombin time (dTT) assay was normal (26.4s), whereas the aPTT remained prolonged (53.9s) after 11 hours of argatroban infusion. Taking these limitations of aPTT into account, we believe that it is to understand the relationship between the aPTT and argatroban concentration in patients (e.g., where aPTT baseline is prolonged) during the early stages of therapy and to monitor some patients by quantifying the plasma argatroban levels. In addition, we have demonstrated that there are different sensitivities to argatroban with different aPTT reagents in samples collected from patients during argatroban therapy⁹ and in spiked plasma prepared by addition of drug to plasma in vitro.¹⁰ In our study of patient samples,⁹ the reagent least sensitive to argatroban (among six reagents studied) was Actin FSL (with a mean ratio of 1.6 in 57 patient samples) with the most sensitive being SynFAX (with mean aPTT ratio of 2.3). The correlation between aPTT ratio and argatroban concentration was poor for all six reagents ($r = 0.07–0.29$), and we have demonstrated that the correlation between argatroban and aPTT is different from analyses of ex vivo samples versus in vitro spiking.¹⁰ In 57 patient samples⁹ with a mean argatroban concentration of 0.43 µg/mL, the mean aPTT ratio using Actin FSL was 1.58, whereas in spiked samples an aPTT ratio of 1.5 with the same reagent corresponded to a much higher argatroban concentration of 0.84 µg/mL; accordingly, we strongly agree with Van Cott et al¹ that the use of assay calibrators and spiked plasmas should

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not be recommended for assessing target ranges for a particular aPTT method.

We would also like to use this opportunity to share new data. In previous work, we have demonstrated a discrepancy in aPTT ratio with different reagents. Also, with one of our argatroban administered patients, argatroban levels were determined using Hemoclot thrombin inhibitor (HTI) Assay (Hyphen Biomed Neuville-sur-Oise, France). Prior to argatroban administration we measured and saw a difference in their baseline aPTT ratios using Actin FS (ratio 1.9) and SynthASil (ratio: 1.1). During argatroban therapy the patient had a mean argatroban level of 1.04 µg/mL (range: 0.5–1.76 µg/mL), corresponding to different aPTT ratios with different reagents (Actin FS, mean (range) ratio of 3.1 (2.1–4.1); SynthAsil, mean (range) ratio of 1.6 (1.1–2.1)). Thus, some of these results would have suggested the patient was over-anticoagulated (if the Actin FS was used for monitoring, thereby indicating the dose should be reduced), whereas no action would be taken if using SynthAsil. In our previous data,⁹ we demonstrated that SynthAsil and Actin FSL had similar low aPTT ratios with patients on argatroban, whereas Actin FS gave higher aPTT ratios in patient samples. Actin FSL was used in the initial trial of healthy patients, which gave rise to the aPTT ratio range of 1.5 to 3 times baseline aPTT.⁵

One important problem with the use of argatroban assays for monitoring is the lack of studies in which a therapeutic range has been established using clinical outcomes. This means there is no consensus on what the argatroban therapeutic range concentration should be. For example, Love et al¹¹ cite a therapeutic range by dilute thrombin time as being nearly 55 to 98 seconds, based on spiked samples of 0.2 to 2.2 µg/mL. The upper value is higher than any other observed value we found in our literature review.¹⁰ Van Cott et al¹ describe a tentative proposed range of 0.6 to 1.8 µg/mL. The lower level of 0.6 µg/mL is higher than any we have seen in the literature. The most recently cited range extrapolated that utilizing the HTI gave rise to a range of 0.25 to 1.5 µg/mL.¹² A recent publication has considered clinical outcomes and also compared the aPTT to chromogenic anti-IIa assay and cites a range of 0.4 to 1.2 µg/mL for that particular assay.¹³ The authors described new thrombosis cases with prolonged baseline aPTT and concluded that monitoring should use anti-IIa activity rather than aPTT.

In our experience, HTI is a very robust assay and produces very reproducible results (in house reproducibility demonstrated CVs of 2.9–4.6%). Linearity of the calibration curve is 0 to 1.95 µg/mL ($r^2 = 0.999$), with a lower limit of quantification (LLQ) determined as 0.03 µg/mL (we recommend checking the [LLQ] for each new lot of reagent). We agree that there is no agreed therapeutic range for argatroban by drug concentration, but this is not sufficient reason to

rely solely on the aPTT. It is also of concern that some recommendations utilize 100 seconds as a cutoff because we have demonstrated,⁹ as have others,¹¹ that this may sometimes lie within the therapeutic range of 1.5 to 3 by aPTT ratio. More data are needed to link argatroban concentrations to clinical outcomes during therapy for heparin-induced thrombocytopenia (HIT). In the meantime, aPTT results during argatroban therapy should be interpreted with caution, and determination of argatroban concentration by a calibrated quantitative assay can give useful additional information.

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