CASE REPORT

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Novel Monitoring and Dose Adjustment of Argatroban, a Direct Thrombin Inhibitor, to Maintain Therapeutic Anticoagulation in a Patient With Antiphospholipid Antibody Syndrome, Heparin-Induced Thrombocytopenia, and COVID-19 Pneumonia

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BACKGROUND: In patients who require systemic anticoagulation, a reliable monitoring method is required to ensure anticoagulation is maintained within the correct therapeutic window and patients are treated appropriately. When titrating direct thrombin inhibitors (DTIs), dilute thrombin time (dTT) measurements have been demonstrated to be more reliable and accurate than activated partial thromboplastin time (aPTT) measurements and thus often the preferred DTI assessment. However, a clinical need arises when both dTT measurements are not readily available and aPTT measurements are unreliable.

CASE SUMMARY: A 57-year-old woman with a history of antiphospholipid antibody syndrome, heparin-induced thrombocytopenia, and multiple prior deep venous thromboses and pulmonary emboli was admitted with COVID-19 pneumonia and intubated due to hypoxic respiratory failure. Argatroban was initiated in place of her home medication warfarin. However, the patient had a prolonged aPTT value at baseline and overnight dTT assay measurements were limited at our institution. A multidisciplinary team of hematology and pharmacy clinicians created a modified patient-specific aPTT target range and argatroban dosing was titrated accordingly. Subsequent aPTT values in the modified target range corresponded to therapeutic dTT values, indicating therapeutic anticoagulation was successfully achieved and maintained. Patient blood samples were additionally evaluated retrospectively using an investigational novel point-of-care test that detected and quantified the argatroban anticoagulant effect.

CONCLUSIONS: Therapeutic anticoagulation with a DTI in a patient with unreliable aPTT measurements can be achieved with use of a modified patient-specific aPTT target range. Early validation of an investigational rapid testing alternative for DTI monitoring is promising.

KEY WORDS: activated partial thromboplastin time; argatroban; COVID-19; dilute thrombin time; direct thrombin inhibitor

CASE PRESENTATION

A 57-year-old woman with a history of antiphospholipid antibody syndrome, heparin-induced thrombocytopenia (HIT), and multiple prior deep venous thromboses and pulmonary emboli was admitted with COVID-19 pneumonia and intubated due to hypoxic respiratory failure. She later provided verbal consent for inclusion of her anonymized data in this case report. In place of

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her home medication warfarin, argatroban was initiated at a rate of 1 µg/kg/min. The patient's weight was 140.8 kg. Argatroban was chosen for systemic anticoagulation given her history of HIT and the need for an anticoagulation agent with a short half-life in the setting of critical illness and ongoing procedures. This patient had a prolonged activated partial thromboplastin time (aPTT) value at baseline of 39.0 seconds, which was likely due to measurement interference from the presence of a positive lupus anticoagulant. Given this baseline elevation, an alternate monitoring parameter was needed for reliable anticoagulation management.

aPTT and dilute thrombin time (dTT) measurements from patient plasma samples were completed by standard assay at the Massachusetts General Hospital Coagulation Laboratory. At our institution, the standard target range of aPTT values in patients on therapeutic anticoagulation is 66–86 seconds, and the standard target range of dTT values in patients on therapeutic argatroban is 47–99 seconds.

Following argatroban initiation, a subsequent aPTT was obtained at 89.3 seconds, which falls slightly above the standard target therapeutic range of our institution's assay. However, this value corresponded to a dTT measurement of only 39.2 seconds, which is below the target therapeutic range (**Fig. 1**). Thus, our institutional standard aPTT target range could not be used to reliably maintain therapeutic anticoagulation for this patient. Although dTT values would have therefore been the preferred measurement for argatroban dose titration in this situation, dTT assay measurements were unavailable at our institution overnight, thereby limiting continuous serial use.

To overcome this challenge, a multidisciplinary team of hematology and pharmacy clinicians created a modified aPTT algorithm. By integrating simultaneous aPTT and dTT measurements from patient plasma samples, a patient-specific aPTT target range of 115–135 seconds was derived. Argatroban dosing was titrated accordingly to this target range. Subsequent aPTT values in the modified target range corresponded to therapeutic dTT values, indicating therapeutic anticoagulation was successfully achieved and maintained (Fig. 1).

Excess patient samples were also evaluated retrospectively using a novel investigational point-of-care (POC) coagulation test to detect and quantify the effect of argatroban (Coagulo Medical Technologies, Boston, MA). This assay uses less than 50 microliters of blood sample and requires 10 minutes to perform. A reference Clotting Time Score (CTS) curve for argatroban was derived using spiked healthy adult samples and a factor IIa CTS was computed for each sample tested (1, 2). Comparison of CTS and dTT values demonstrated moderate positive linear correlation between test results, with a Pearson's correlation *r* value of 0.824 (95% CI, 0.285–0.967; **Fig. 2**). All factor IIa CTS results accurately reflected if argatroban dosing achieved an appropriate level of anticoagulation (Fig. 2).

DISCUSSION

In patients who require systemic anticoagulation, a reliable monitoring method is required to ensure anticoagulation is maintained within the correct therapeutic window and patients are treated appropriately. Often, aPTT measurements are used when titrating therapies such as IV heparin or direct thrombin inhibitors (DTIs). However, several case series have shown there can be poor correlation of aPTT values with both DTI plasma concentration levels as well as other

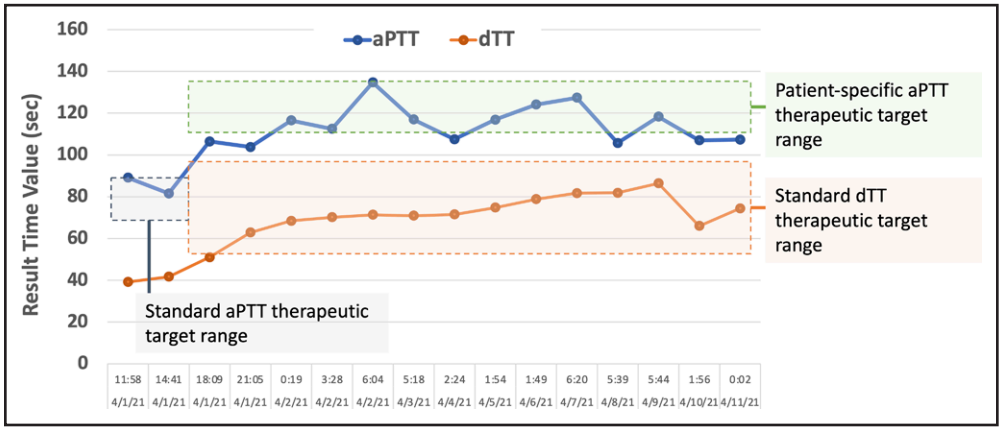

Figure 1. Serial-activated partial thromboplastin time (aPTT) and dilute thrombin time (dTT) measurements at simultaneous timepoints. Initial aPTT values fell within a standard aPTT therapeutic target range; however, corresponding dTT values indicated target anticoagulation was not achieved. Subsequent titration of argatroban to a patient-specific aPTT therapeutic target range achieved therapeutic dTT levels.

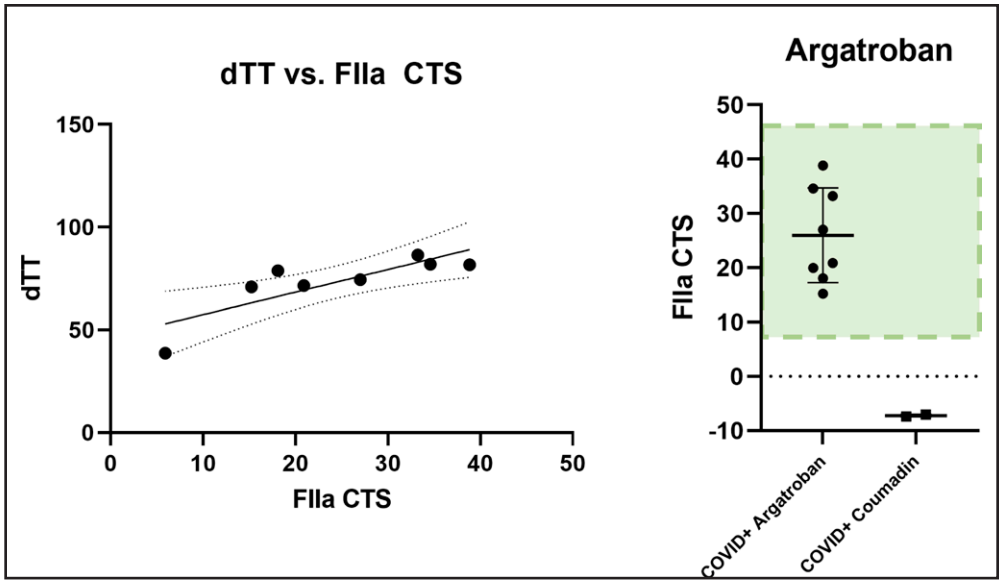

Figure 2. Moderate correlation observed between serial dilute thrombin time (dTT) measurements and factor IIa (FIIa) Clotting Time Scores (CTSs) at simultaneous timepoints, with all FIIa CTS values accurately reflecting if argatroban dosing achieved an appropriate level of anticoagulation. Patient blood samples were evaluated retrospectively using a novel point-of-care coagulation test to detect and quantify the effect of argatroban (Coagulo Medical Technologies, Boston, MA), with an FIIa CTS derived for each simultaneous dTT measurement timepoint. All FIIa CTS values that fell within the target argatroban concentration range (0.4–2.0 μg/L) were within FIIa CTS target range (6.6–47.3). FIIa CTS values were appropriately negative in the samples collected at time points of treatment with warfarin only.

anticoagulant measurement assay results, and a dTT has been established as an alternative (3–6). One such study was an early in vitro study conducted by Love et al (3) in which blood samples were drawn from 63 patients and spiked with varying concentrations of argatroban, bivalirudin, and lepirudin. The aPTT failed to accurately reflect DTI concentration in almost half of the samples, all of which were drawn from patients with lupus inhibitors, low vitamin K-dependent factors, or elevated D-dimer levels. In contrast, the dTT was not affected by these same conditions. There was a linear and dose-dependent effect when evaluating DTI doses and dTT levels in these same patient blood samples, establishing that dTT measurements were more consistent and a viable alternative to aPTT monitoring in patients with the aforementioned conditions (3).

Results from additional observational studies carried out on plasma samples from patients on active treatment with a DTI have demonstrated there can be poor concordance between the aPTT and other anticoagulant measurement assays, particularly in critically ill patients (4–7). In a recent larger observational study conducted by Beyer et al (6), aPTT, dTT, and ecarin chromogenic assay levels were measured in 198 plasma samples from 101 hospitalized patients treated with argatroban or bivalirudin to assess concordance between results from these three assays. Discordant levels were further analyzed by liquid chromatography with tandem mass spectrometry (LC MS/MS). Overall, discordant assay results occurred in 59% of patients treated with DTIs and discordance between aPTT and dTT levels occurred frequently, being observed in 45% and 43% of bivalirudin and argatroban samples, respectively. Notably, over 85% of patients included in this study were in the ICU at the time of DTI initiation. Comparison of characteristics between patients with discordant versus concordant results revealed no statistically significant difference with respect to gender, age, clinical indication for DTI use, or baseline PTT elevation status. However, there was a statistically significant difference in average weight between the two patient groups; patients with discordant results were on average 8 kg heavier (87 vs 79 kg). When samples were further analyzed by LC MS/MS, the results were more likely to be concordant with the dTT versus aPTT results for both bivalirudin and argatroban-treated samples (6). An additional recent study, specifically in three patients with COVID-19 suggested unreliability of the aPTT in monitoring argatroban (8). In total, these studies demonstrate that dTT levels, in contrast to aPTT levels, can be a more consistent measure of anticoagulant effect in certain patients treated with DTIs. These observational results suggest that critically ill patients and those with increased weight, in particular, are at potentially higher risk for measurement discordance.

Overall, there is a clinical need for a readily available and consistently accurate DTI monitoring assay, especially in clinical settings where studies have shown aPTT may be unreliable, including antiphospholipid antibody syndrome, COVID-19

infections, and obesity. Although a dTT is perhaps the preferred measurement in terms of reliability and accuracy compared with aPTT, due to limited hospital resources and assay accessibility, dTT measurements are not always readily available. This restraint, in turn, makes accurate DTI dose adjustment challenging. Here, we present an alternative approach wherein limited available dTT measurements guided derivation of a patient-specific modified aPTT scale that was then implemented to titrate argatroban dosing. Target anticoagulation effect was retrospectively confirmed by corresponding dTT measurements that fell within the therapeutic dTT target range. Successful collaboration of a multidisciplinary team was key to achieving the accurate real-time argatroban dosing adjustments necessary to maintain therapeutic anticoagulation. Although the aPTT target range was patient-specific based on simultaneous aPTT and dTT measurements from this individual's plasma samples, the process by which this was achieved lays the foundation to potentially conduct similar comparisons in similarly complex patients with the overall goal to derive a protocol that could be extrapolated universally.

We also report early validation of an investigational novel test that could offer a rapid, POC measurement of DTI effect. Although our results in this case report are limited, being from a small number of blood samples from a single patient, they lay the foundation for future investigation and validation testing. This novel assay, which detects and quantifies the anticoagulant effect of argatroban, could improve patient care by enabling accurate titration of DTIs when both aPTT measurements are unreliable and dTT measurements are not readily available.

In conclusion, while therapeutic anticoagulation with a DTI in a patient with unreliable aPTT measurements is challenging, it can be achieved with multidisciplinary collaborative care and patient-specific dose adjustments. Early validation of a novel rapid POC test to quantify argatroban effect is promising. Such a technology could dramatically improve accurate titration of DTIs to maintain therapeutic anticoagulation.

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REFERENCES

1. Frydman GH, Rosovsky RP, Lee J, et al: Abstract 12966: Novel, low-volume, point-of-care coagulation test successfully detects anticoagulation resistance in hospitalized patients with COVID-19. *Circulation* 2021; 144:A12966–A12966
2. Frydman GH, Berger BM, Kostousov V, et al: Novel coagulation test detects anticoagulation resistance and is associated with thrombotic events in pediatric patients requiring extracorporeal membrane oxygenation. *Crit Care Explor* 2022; 4:e0776
3. Love JE, Ferrell C, Chandler WL: Monitoring direct thrombin inhibitors with a plasma diluted thrombin time. *Thromb Haemost* 2007; 98:234–242
4. Lind SE, Boyle ME, Fisher S, et al: Comparison of the aPTT with alternative tests for monitoring direct thrombin inhibitors in patient samples. *Am J Clin Pathol* 2014; 141:665–674
5. Keyl C, Lehane C, Zimmer E, et al: Monitoring anticoagulation with argatroban in critically ill patients: Activated partial thromboplastin time versus diluted thrombin time. *Thromb Haemost* 2016; 116:1180–1181
6. Beyer JT, Lind SE, Fisher S, et al: Evaluation of intravenous direct thrombin inhibitor monitoring tests: Correlation with plasma concentrations and clinical outcomes in hospitalized patients. *J Thromb Thrombolysis* 2020; 49:259–267
7. Wanat MA, Hart SR, Putney D, et al: Alternative monitoring of argatroban using plasma-diluted thrombin time. *Ann Pharmacother* 2013; 47:e18
8. Guy S, Kitchen S, Makris M, et al: Caution in using the activated partial thromboplastin time to monitor argatroban in COVID-19 and vaccine-induced immune thrombocytopenia and thrombosis (VITT). *Clin Appl Thromb Hemost* 2021; 27:10760296211066945