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Caution in Using the Activated Partial Thromboplastin Time to Monitor Argatroban in COVID-19 and Vaccine-Induced Immune Thrombocytopenia and Thrombosis (VITT)

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Abstract

Introduction: Argatroban is licensed for patients with heparin-induced thrombocytopenia and is conventionally monitored by activated partial thromboplastin time (APTT) ratio. The target range is 1.5 to 3.0 times the patients' baseline APTT and not exceeding 100 s, however this baseline is not always known. APTT is known to plateau at higher levels of argatroban, and is influenced by coagulopathies, lupus anticoagulant and raised FVIII levels. It has been used as a treatment for COVID-19 and Vaccine-induced Immune Thrombocytopenia and Thrombosis (VITT). Some recent publications have favored the use of anti-IIa methods to determine the plasma drug concentration of argatroban.

Methods: Plasma of 60 samples from 3 COVID-19 patients and 54 samples from 5 VITT patients were tested by APTT ratio and anti-IIa method (dilute thrombin time dTT). Actin FS APTT ratios were derived from the baseline APTT of the patient and the mean normal APTT.

Results: Mean APTT ratio derived from baseline was 1.71 (COVID-19), 1.33 (VITT) compared to APTT ratio by mean normal 1.65 (COVID-19), 1.48 (VITT). dTT mean concentration was 0.64 µg/ml (COVID-19) 0.53 µg/ml (VITT) with poor correlations to COVID-19 baseline APTT ratio $r^2 = 0.1526$ $p < 0.0001$, mean normal $r^2 = 0.2188$ $p < 0.0001$; VITT baseline APTT ratio $r^2 = 0.04$ $p < 0.001$, VITT mean normal $r^2 = 0.0064$ $p < 0.001$.

Conclusions: We believe that dTT is a superior method to monitor the concentration of argatroban, we have demonstrated significant differences between APTT ratios and dTT levels, which could have clinical impact. This is especially so in COVID-19 and VITT.

Keywords
COVID-19, VITT, argatroban, APTT, dilute thrombin time

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Introduction

Argatroban is licensed for use in patients with Heparin induced thrombocytopenia (HIT) and more recently it has been used in COVID-19 patients and Vaccine-induced Immune Thrombocytopenia (VITT). The summary of product characteristics (SmPC) advises users to monitor this anticoagulant using the activated partial thromboplastin time (APTT) with a target range of 1.5 to 3.0 times the initial baseline value but not exceeding 100 s.[1] This baseline APTT, however, is not

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always available or known.[2] The recommended range is based on a trial which used the APTT reagent Actin FSL in 73 healthy volunteers.[3] Limitations of the APTT for monitoring argatroban have been reported in several publications.[4,5] Despite this, both the British Committee for Standards in Haematology[6] and the American College of Chest Physicians[7] guidelines suggest users monitor the anticoagulation through the APTT ratio. Keyl et al.[8] showed that in critically ill patients on argatroban there is a poor correlation between APTT values and drug concentration ($r^2 = 0.28$) with a flattening of the dose response with increasing argatroban concentration. The APTT is known to plateau at higher levels of argatroban. In contrast, the dTT (dilute thrombin time) Hemoclot thrombin inhibitor assay (HTI) shows a linear relationship ($r^2 = 0.84$) making it a preferable monitoring method.[8]

French guidance on HIT management and monitoring[9] suggests that anti-IIa methods are more appropriate than APTT and proposed a therapeutic range of 0.5 to 1.5ug/ml but also reference a range of 0.25 to 1.5ug/ml (derived by control plasma spiked with argatroban using HTI) Tardy-Poncet et al.[10] The Swiss guidance[11] cites 0.4 to 1.5ug/ml as a target for therapy and recommend the use of monitoring by anti-IIa assay, with or without the APTT, adding the caveat that the target range for various assays has not been established in an outcome-based setting. This range maybe based on earlier work of Colucci et al.[12] who established that range with spiked plasma comparing the APTT ratio (by Pathromtin SL) corresponding to a range of argatroban concentrations. We have previously published patient data[5] showing that Pathromtin SL gave rise to a mean APTT ratio 2.13 and a poor correlation to dTT (HTI) ($r^2 = 0.10$). APTT testing with Actin FSL gave a mean ratio of 1.58 (correlation to dTT [HTI]) was slightly better at $r^2 = 0.29$. These reagent dependent differences in APTT ratio mean that a therapeutic range established by identifying the concentration of drug corresponding to APTT therapeutic range would be different for different APTT reagents. It could be safer to use a range which considered efficacy and safety such as the range suggested by Vu et al.[13] which was based on a retrospective patient study on argatroban comparing monitoring by APTT and a chromogenic anti-IIa assay giving rise to this range of 0.4 −1.2 μg/ml.

The British Society of Haematology Vaccine-induced Immune Thrombocytopenia and Thrombosis (VITT) guidance produced by their Expert Haematology Panel[14] permits use of argatroban to anticoagulate probable cases of VITT and state "Argatroban levels should ideally monitored by a direct thrombin inhibitor assay if available eg, Hemoclot as APTT correlates poorly with the argatroban effect due to high levels of Factor VIII'.

In the present study we are reporting data on a cohort of 3 COVID-19 patients with HIT (n- = 60) and 5 VITT patients (n = 54) who were being treated with argatroban and who have had measurements of the APTT ratios derived from the patients baseline APTT and the mean normal APTT. In addition the argatroban plasma concentration was measured using dTT.

Methods

Plasma from COVID-19 infected (60 samples) from 3 patients with positive HIT and VITT patients (54 samples) from 5 patients receiving argatroban were collected in 0.109 M citrate BD vacutainer (Becton Dickinson, Franklin Lakes, NJ, USA) centrifuged at 1700 g for 10 min. Consecutive patients were included where samples were available. Tests were performed either as requested for patient management or were performed on anonymized residual plasma in accordance with local ethical approval. Plasma was tested on Sysmex CS51000i (Sysmex, Milton Keynes UK) with APTT reagent Actin FS (Siemens, Erlangen, Germany). APTT Ratios were derived from the mean of normal APTT for the Actin FS (n = 20) – (which is common practice in routine monitoring) as well as the patient's baseline APTT in accordance with the SmPC. The argatroban concentration was determined using the dTT (HTI) (Hyphen Biomed, Neuville-sur–Oise, France) with stored calibration curve (Hyphen Biomed argatroban calibrator). The dTT uses a 1 in 8 dilution in Owrens Veronal Buffer, one part of this dilution is tested with two parts normal pooled plasma, followed by the addition of α thrombin (containing calcium); the clotting time in seconds is proportional to the concentration of argatroban in the test plasma.

Instat version 3.05 (GraphPad Software Inc, San Diego, CA, USA) and GraphPad Prism 8 (GraphPad Software Inc) were used to perform the statistical analysis.

Results

Patient demographics are given in Table 1 along with baseline clotting screen and Acustar HIT results for 3 COVID-19 patients and for the 5 VITT patients the Acustar HIT results alongside the Hyphen Zymutest HIA IgG and Stago Asserchrom HIT IgG ELISA methods. The patient and samples are a low number because argatroban is indicated in very infrequent circumstances like HIT or VITT suspicion. The results are shown in Table 2 as mean results and in Table 3 as concordant and discordant with respect to APTT / argatroban level and therapeutic range. The mean APTT ratio derived according to SmPC from the baseline APTT of the patient: COVID-19 1.71 and VITT 1.33, compared to APTT ratio (derived from mean normal APTT): COVID-19 1.65 and VITT 1.48. The plasma drug concentration quantified by dTT had a mean of 0.64 μg/ml in COVID-19 and 0.53 μg/ml in VITT. Poor correlations were seen in both methods for deriving APTT ratio when compared to dTT COVID-19 baseline APTT ratio $r^2 = 0.1526$ $p < 0.0001$, mean normal $r^2 = 0.2188$ $p < 0.0001$; VITT baseline APTT ratio $r^2 = 0.04$ $p < 0.001$, VITT mean normal $r^2 = 0.0064$ $p < 0.001$. Table 3 defines concordant and discordant results by APTT ratio and argatroban concentration, concordant are therefore samples with APTT ratio of 1.5 - 3.0 and argatroban concentration of 0.4 - 1.2 μg/ml (based on Vu et al.[13] cited range) or where both the APTT ratio and argatroban concentration are sub-therapeutic (<1.5 and 0.4 μg/ml) or supra-therapeutic (>3.0 and 1.2 μg/ml) these are shown as bold.

From the data shown in Table 2 the correlation between baseline APTT and mean normal APTT for the COVID-19

Table 1. Gives the patients demographics including Sex, Age group, number of samples tested, with the additional baseline Clotting Screen and HIT methods used for diagnosis of HIT or VITT. Due to the nature of the patient cohorts some patients had larger samples sizes, no samples were taken during bridging to warfarin or any other anticoagulants.

Patient	Sex	Age group	N	Baseline Clotting Screen and HIT methods (normal range stated in brackets for clotting screen parameter)
C19-1	Female	50 to 60	16	PT 10.4 s (9.8-11.8 s) APTT 22.5 s (20.0-28.5 s) Fibrinogen 4.0 g/L (2.0-4.0 g/L) Acustar HIT 1.65u/mL
C19-2	Male	60 to 70	18	PT 11.3 s (9.8-11.8 s) APTT 23.7 s (19.2-27.9 s) Fibrinogen 6.6 g/L (2.0-4.0 g/L) Acustar HIT 19.65u/mL
C19-3	Female	70 to 80	26	PT 11.1 s (9.8-11.8 s) APTT 21.7 s (19.2-27.9 s) Fibrinogen 8.1 g/L (2.0-4.0 g/L) Acustar HIT 5.35u/mL
VITT-1	Female	50 to 60	1	PT 11.7 s (9.8-11.6 s) APTT 22.5 s (19.2-27.9 s) Fibrinogen 1.8 g/L (2.0-4.0 g/L) D-Dimer 29503 µg/L Acustar HIT 0.05 u/mL Hyphen HIT IgG 0.035OD* Stago Asserchrom HIT IgG 0.078 OD* * VITT diagnosed clinically.
VITT-2	Male	20 to 30	11	PT 12.2 s (9.8-11.6 s) APTT 24.8 s (19.2-27.9 s) Fibrinogen 1.2 g/L (2.0-4.0 g/L) D-Dimer 29881 µg/L
VITT-3	Female	60 to 70	4	PT 11.1 s (9.8-11.6 s) APTT 23.9 s (19.2-27.9 s) Fibrinogen 5.5 g/L (2.0-4.0 g/L) Acustar HIT 0.05u/mL Hyphen HIT IgG Elisa 0.052OD Stago Asserchrom HIT IgG 0.297OD
VITT-4	Female	40 to 50	36	PT 13.1 s (9.8-11.6 s) APTT 27.3 s (19.2-27.9 s) Fibrinogen 1.1 g/L (2.0-4.0 g/L) D-Dimer >50,000 µg/L Acustar HIT 0.48u/mL Hyphen HIT IgG 2.399OD Stago Asserchrom HIT IgG 3.311 OD
VITT-5	Male	30 to 40	2	PT 14.6 s (9.8-11.6 s) APTT 21.4 s (19.2-27.9 s) Fibrinogen 1.0 g/L (2.0-4.0 g/L) D-Dimer >50,000 µg/L Hyphen HIT IgG 0.420 OD

Acustar HIT = HemosIL Acustar HIT IgG Chemiluminescent method not sensitive for VITT; normal range 0 −1.0u/mL
Hyphen HIT IgG = Hyphen Zymutest HIA IgG – ELISA method suitable for VITT detection; normal range 0 −0.239 OD
Stago Asserchrom HPIA IgG – ELISA method suitable for VITT detection; normal range 0 to 0.238 OD
Normal ranges for PT and APTT are reagent lot specific hence different ranges given.

cohort $r^2 = 0.9382$ $p < 0.0001$; VITT $r^2 = 0.9201$ $p < 0.0001$ although statistically significant they are low and not clinically relevant.

Table 3 demonstrates that the poor correlation significantly influences clinical management. Focusing on the use of baseline APTT as recommended by SmPC 13/19 samples in the COVID-19 cohort and 21/36 in the VITT cohort had therapeutic dTT levels despite an APTT ratio <1.5. Monitoring by APTT ratio would have resulted in unnecessary increase in the argatroban infusion rate. Conversely 8/40 in the COVID-19 cohort and 3/18 in the VITT cohort samples had subtherapeutic dTT levels despite therapeutic APTT ratio and therefore potentially would have been under anticoagulated. Finally, 3 samples in the COVID-19 cohort had dTT levels >1.4 µg/ml: 1 being sub therapeutic and the remaining two had therapeutic APTT ratios. Figures 1 and 2 shows the relationship between the APTT ratios and dTT.

Table 2. Mean APTT in Ratios of 60 samples from 3 COVID-19 patients; and 54 samples from 5 VITT patients receiving argatroban and the correlation of these APTT ratios to the dTT (HTI). APTT ratios were calculated using patient baseline and mean normal APTT. Comparison of the two patients from the two cohorts with the most samples tested is also given. P value given is for a two-tailed paired t test, showing extremely significant differences.

	Argatroban µg/ml	Baseline Actin FS ratio	Actin FS mean normal ratio	Correlation of baseline Actin FS ratio to dTT	Correlation of mean normal Actin FS ratio to dTT
COVID−19 samples (n = 60) Mean (range)	0.64 (0.08-2.70)	1.71 (1.07-3.10)	1.65 (1.02-2.86)	$R^2 = 0.1526$	$R^2 = 0.2188$
Case C19-3 Samples (26) Mean (range)	0.84 (0.41-2.70)	1.74 (1.24-3.10)	1.60 (1.14-2.86)	$R^2 = 0.9331$	$R^2 = 0.9326$
VITT samples (n = 54) Mean (range)	0.53 (0.06-1.11)	1.33 (0.68-1.90)	1.48 (0.79-1.94)	$R^2 = 0.04$	$R^2 = 0.0064$
Case VITT-4 Samples (36) Mean (range)	0.47 (0.11-0.78)	1.18 (0.68-1.56)	1.37 (0.79-1.81)	$R^2 = 0.2677$	$R^2 = 0.2719$

Discussion

Argatroban is recommended to be monitored by APTT according to the SmPC;[1] we have demonstrated in previous publications that the APTT has limitations for monitoring argatroban.[4,5] In this present study we are reporting data from two patient cohorts receiving argatroban (COVID-19 and VITT),

Table 3. Concordant result in bold indicate both APTT ratio and argatroban concentration were sub- therapeutic, therapeutic or supra-therapeutic. APTT ratios were calculated using patient's baseline and mean normal APTT. Shows the Concordant (highlighted in BOLD) and discordant APTT ratios and dTT plasma drug concentration to argatroban for COVID-19 cohort and VITT cohort utilizing both the ratio obtained by utilizing the patients' baseline APTT or by using the mean normal for the APTT. ie APTT baseline <1.5 argatroban <0.4 = 5 samples out of 19 APTT ratios of <1.5 were discordant.

	Argatroban < 0.4	**Argatroban 0.4 to 1.2**	Argatroban >1.2		Argatroban < 0.4	**Argatroban 0.4 to 1.2**	Argatroban >1.2
COVID-19				**COVID-19**			
APTT <1.5 Baseline ratio (n = 19)	**5/19**	13/19	1/19	APTT <1.5 Mean normal ratio (n = 24)	**5/24**	19/24	0/24
APTT 1.5 to 3.0 Baseline ratio (n = 40)	8/40	**30/40**	2/40	APTT 1.5 to 3.0 Mean normal ratio (n = 36)	8/36	**24/36**	4/36
APTT >3.0 Baseline ratio (n = 1)	0/1	0/1	**1/1**	APTT >3.0 Mean normal ratio (n = 0)	0/0	0/0	**0/0**
VITT				**VITT**			
APTT <1.5 Baseline ratio (n = 36)	**15/36**	21/36	0/36	APTT <1.5 Mean normal ratio (n = 26)	**6/26**	20/26	0/26
APTT 1.5 to 3.0 Baseline ratio (n = 18)	3/18	**15/18**	0/18	APTT 1.5 to 3.0 Mean normal ratio (n = 28)	12/28	**16/28**	0/28
APTT >3.0 Baseline ratio (n = 0)	0/0	0/0	**0/0**	APTT >3.0 Mean normal ratio (n = 0)	0/0	0/0	**0/0**

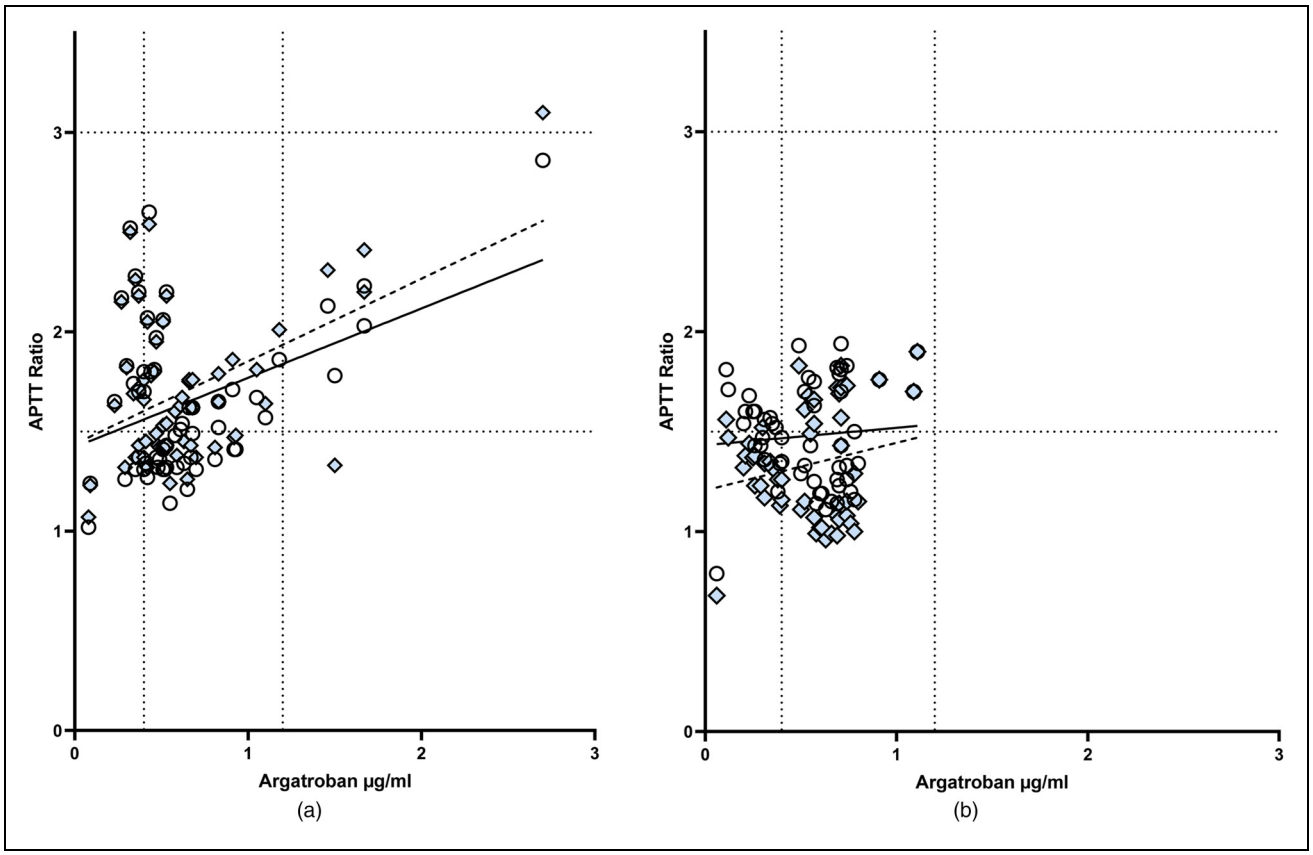

Figure 1. (a) shows the relationship between APTT ratios (by mean normal or patient baseline) and dTT in 3 COVID-19 patients receiving argatroban. Each point is a single APTT ratio/argatroban measurement: Open circles represents mean normal APTT ratio (regression line solid), Blue diamonds represent patients baseline APTT ratio (regression line dashes). Dotted lines denotes the therapeutic range by both APTT ratio and argatroban. (b) shows the relationship between APTT ratios (by mean normal or patient baseline) and dTT in 5 VITT patients receiving argatroban. Each point is a single APTT ratio/argatroban measurement: Open circles represents mean normal APTT ratio (regression line solid), Blue diamonds represent patients baseline APTT ratio (regression line dashes). Dotted lines denotes the therapeutic range by both APTT ratio and argatroban.

the SmPC[1] defines the APTT to be 1.5 to 3 times the baseline value of the patients APTT however it is not always available or known,[2] we investigated if there was a clinical difference if the baseline APTT was used to derive the APTT ratio or the mean normal APTT.

Several anti-IIa methods have been described in the literature for measuring argatroban[15,16] with the exception of LC MS/MS they can be easily performed in most specialized Coagulation/ Haemostasis laboratories. Beyer et al.[16] has shown that dTT correlated well ($r^2 = 0.8428$) with LC MS/MS, the HTI dTT method has also the benefit of having a commercially available standard[15] although in-house argatroban calibrators can be produced using normal plasma spiked with argatroban where commercial calibrators are unavailable. Another advantage of dTT levels is that they are not impacted by the plateau seen with the APTT measurements. We have seen this plateau effect in two samples received by our laboratory had very high argatroban levels, later confirmed to have been samples taken from the arm with the argatroban infusion. The APTT ratios of 4.17 and 3.66 corresponded to dTT levels of 14.8 µg/ml and 4.86 µg/ml respectively.

Others have previously described argatroban resistance in patients which has been caused by increased levels of Factor VIII where the APTT has stayed the same despite increasing the dose of argatroban.[17,18] McGlynn et al.[19] specifically demonstrated a COVID-19 patient treated with argatroban with Factor VIII 477 IU/dL, which had baseline APTT 23 s. Factor VIII assays (FVIII:C) were not performed on all the samples in the data provided and this is a limitation in the study; however one of COVID-19 patient and one VITT patient had a FVIII:C performed utilizing the Biophen Chromogenic FVIII Assay, (Hyphen Biomed, Neuville-sur–Oise, France, normal range 62 to 199 IU/dL). COVID-19 patient had FVIII: C 458 IU/dL with a corresponding argatroban level of 0.51 µg/ml with an APTT 33.2 s (normal range 19.2- 28.5 s), baseline APTT ratio 1.53, mean normal APTT ratio 1.41, dosing may have been altered if the APTT ratios were used as they were around the lower target of therapeutic range despite therapeutic argatroban levels. The VITT patient had FVIII:C 294 IU/dL with a corresponding argatroban level of 0.78 µg/ml, APTT 27.2 s, baseline APTT ratio 1.00, mean normal APTT ratio 1.16, this high FVIII:C level is reducing

the APTT and would lead the clinician to increasing the argatroban infusion unnecessarily.

For all patients except one we targeted therapeutic anticoagulation with argatroban. In one VITT case with cerebral vein thrombosis, extensive intracerebral haemorrhage and thrombocytopenia the argatroban was used at the critical illness concentration without dose escalation.

With respect to how the APTT ratio is derived there is little difference between the mean results obtained: COVID-19 baseline APTT 1.71 v mean normal 1.65; although the VITT cohort had mean results below the target therapeutic range (baseline APTT 1.33 v mean normal 1.48) this may reflect that 36 datasets were from the patient targeted with the critical illness concentration without dose escalation whose Factor VIII was also high (294 IU/dL).

Despite most laboratories using the APTT we believe the dTT is superior to monitoring the concentration of argatroban. We have shown significant differences between APTT ratios and dTT levels which would have clinical impact. This is especially so in COVID-19 and VITT where the high FVIII levels can influence the APTT.

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SG, SK, MM, RMM, GVS and JJV designed the study. SG performed the laboratory work, collated the data and wrote the first draft manuscript. SK, MM, RMM, GVS and JJV reviewed the manuscript and approved the final draft. No conflicts of interests for all authors.

Declaration of Conflicting Interests

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