Fibrin monomers to monitor anticoagulation with argatroban in patients with acute heparin induced thrombocytopenia

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INTRODUCTION

Because of its short half-life and hepatic metabolism, argatroban is an alternative anticoagulant of choice in patients with heparin-induced thrombocytopenia (HIT) with renal failure or potential future surgery.

As aPTT and argatroban levels are poorly correlated, monitoring argatroban anticoagulation remains challenging, especially in critically ill patients. Also, no therapeutical range has been defined yet [1, 2].

Soluble fibrin monomers (FM) reflect thrombin activity and are increasingly used to asses hypercoagulable patients. However, the effect of anticoagulation on FM levels remains unknown.

AIM

To study the evolution of FM in patients with suspected acute HIT receiving argatroban.

METHODS

- We retrospectively studied all patients who received argatroban at Bichat Hospital between april 2013 and january 2019.
- Patients with acute HIT who had elevated FM (>70µg/ml) at the start of argatroban therapy were included.
- aPTT was measured with HemosIL aPTT-SP on ACLTOP 700 (Werfen).
- FM were measured using STA® Liatest FM (Diagnostica Stago) on ACLTOP 700 (Werfen).
- Anti-IIa activity was determined using diluted thrombin time with Hemoclot® thrombin inhibitor assay (Hyphen Biomed) on ACLTOP 700 (Werfen).
- Laboratory diagnosis of HIT was based on the level of IgG antibodies against platelet factor 4 / heparin (PF4/H) measured with Zymutest® HIA IgG (Hyphen Biomed) and on the positivity of Heparin-Induced Platelet Agglutination assay (HIPA) performed with at least 2 platelet donors [3].

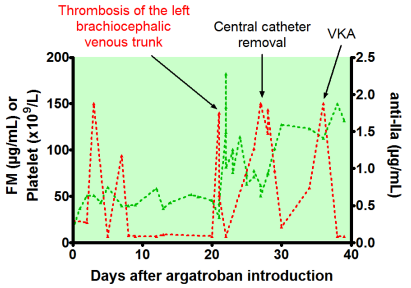
RESULTS

- 11 patients were included :

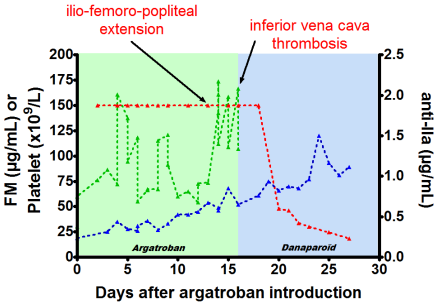
Characteristic	Value
Age, yrs (mean ± SD)	66 ± 13
Sex, no. (%)	
Male	3 (27)
Female	8 (73)
Weight, kg (mean ± SD)	70 ± 16
Clinical context, no. (%)	
Intensive care	3 (27)
Cardiac surgery	8 (73)
Medical	0 (0)
Extra-Corporeal Life Support, no. (%)	4 (36)
Extra-renal epuration, no. (%)	3 (27)
Sepsis, no. (%)	4 (36)
Initial thrombosis, no. (%)	
Arterial	8 (73)
Venous	2 (18)
No thrombosis	1 (9)
Platelet nadir, x 10^9/L (mean ± SD)	38 ± 25
Anti-PF4/H IgG, mU.DO (mean ± SD)	1821 ± 922
HIPA, no. (%)	
Positive	9 (82)
Negative	1 (9)
Not realized	1 (9)
Duration of argatroban treatment, days (mean ± SD)	18 ± 18
Baseline aPTT , sec (mean ± SD)	33.5 ± 7.1
aPTT on the first day of argatroban therapy, sec (mean ± SD)	73.2±38.4
Anti-IIa on the first day of argatroban therapy, µg/mL (mean ± SD)	0.9 ± 0.5

- Mean time of argatroban treatment to reach negative FM (<20µg/ml) was 3.3±2.5 days. Mean aPTT was then 68.2 ± 23.9 sec (ratio 2,5±0.8) and **anti-IIa 1.5 ± 0.8 µg/ml**, which is higher than first-day anti-IIa (p=0.05).
- 4/11 (26%) patients developed **further thrombotic complication** under argatroban therapy. 3/4 (75%) had positive FM when thrombosis occurred (case examples 1 and 2 below)

Case example 1:
72 year old female
Hospitalized for pneumonia and acute renal failure
Endovascular stent-graft placement during hospitalization
Multiple strokes and platelet count fall (nadir 51 G/L) under heparin therapy
Anti-PF4/H IgG 2.740 mU.DO
Positive HIPA



Case example 2:
60 year old female
Hospitalized for lung transplantation
Left femoral vein thrombosis and platelet count fall (nadir 19 G/L) under heparin therapy
Anti-PF4/H IgG 2.609 mU.DO
Positive HIPA



anti-IIa (g/mL)
FM (µg/mL)
platelet count (x10^9/L)

CONCLUSIONS

- **FM become quickly negative under argatroban therapy in the majority of cases.**
- **However, FM that remain positive under argatroban seem to be associated with thrombosis.**
- **Further studies are needed to prospectively evaluate the benefit of FM to monitor argatroban dosage and its clinical efficacy.**

REFERENCES

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