How to Monitor Heparin Therapy. Still a Controversy?

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INTRODUCTION:

- Is the chromogenic anti-factor Xa (anti-Xa) assay less affected by pre-analytical variables in monitoring patients on unfractionated heparin (UFH) and low molecular weight heparin (LMWH) than the activated partial thromboplastin time (APTT)?

INTRODUCTION

- APTT most commonly used assay to monitor UFH therapy. Cannot be used to monitor LMWH therapy.
- Therapeutic range: 1.5-2.5 lab control or mean normal range. Corresponds to 0.3-0.7 U/mL anti-Xa
- Previous studies have cited the interference of oral anticoagulants, oral contraceptives, lupus anticoagulants, factor deficiencies, acute phase reactants (fibrinogen, FVIII), specimen collection, low anti-thrombin, APTT reagent sensitivity, and instrumentation on the APTT.

INTRODUCTION

- Anti-Xa interferences:
  - Hyperbilirubinemia
  - Hyperlipidemia; can be cleared with ultracentrifugation.
  Anti-Xa assay can be used to monitor all heparin analogues and UFH and DOACs.
  Therapeutic range for UFH: 0.3-0.7 U/mL
  LMWH: 0.5-1.1 U/mL

MATERIALS AND METHODS:

- UFH subjects: 10 males and 10 females, 20-85 y/o. Range assayed: 0.05-2.01 IU/ml.
- LMWH subjects: 13 males and 13 females, 26-91 y/o. Range assayed: 0.06-1.22 IU/ml.
- Pre-existing conditions included but not limited to coronary disease, antiphospholipid antibody syndrome, deep vein thrombosis, recurrent spontaneous abortion, pulmonary embolism.
- Some of the subjects were also on oral anticoagulant therapy.

MATERIALS AND METHODS:

- Each subject had 6 vacutainer collection tubes obtained in a single atraumatic venipuncture.
- Specimens were split into 3 groups: 3.8% sodium citrate, 3.2% sodium citrate and a CTAD tube.
- Each tube had a normal draw of 9:1 blood to anticoagulant ratio and a short draw of 6:1.
- Data was analyzed using descriptive statistics, t-test or ANOVA, and linear regression.

MATERIALS AND METHODS:

- Platelet-poor plasma was obtained by centrifuging the whole blood at 2500g for 15 minutes guaranteeing a platelet count of <10,000/uL and stored at –70°C until ready for testing.
- All specimens had an APTT and a chromogenic anti-Xa assay performed on each specimen regardless of the type of heparin being given.
- Each specimen had an anti-Xa assay result for the UFH, LMWH and a HYBRID anti-Xa calibration curve run.

MATERIALS AND METHODS:

- APTT reagent used was the PTT-A® from Diagnostic-Stago, Inc.
- STA-Rotachrom® Heparin Assay, Diagnostic-Stago, Inc.
- Analayzer was an STA-R® automated coagulation analyzer.
- All collection tubes were non-wettable, siliconized glass obtained from BD Vacutainer Systems.

You need 1.5-2.5 X lab control or MNR
George Fritsma 6/20/2011

ANTI-Xa/APTT RESULTS ON UFH SUBJECTS: ANOVA

GROUPS	Ave: IU/ml	Ave: seconds
UFH 3.8 ND	0.36	105.4
UFH 3.8 SD	0.32	127.2
UFH 3.2 ND	0.37	107.7
UFH 3.2 SD	0.33	105.5
UFH CTAD ND	0.37	104.3
UFH CTAD SD	0.36	100.1

Combine this table with the previous table, skip the p values.
George Fritsma, 6/29/2017

SUBJECTS UFH	3.8 ND APTT	3.8 SD APTT	3.2 ND APTT	3.2 SD APTT	CTAD ND APTT	CTAD SD APTT	APTT MEAN (SEC.)	ANTI-FXa MEAN U/ml
6284	36.9	48.9	38.4	41.4	43.3	47.8	42.8	0.41
0297	114.5	109.9	116.2	107.1	112.8	110.9	111.9	0.35
5793	69.1	64.9	66	66	69.6	67.5	67.2	0.29
1130	68.3	90.8	63.1	74.3	64.4	78.2	73.2	0.45
0807	111.2	133.6	118.6	117	110.6	128.6	119.9	0.45
0447	36.4	63.3	35.8	43.6	34.3	51.1	44.1	0.46
0316	70.7	75.6	78.5	69.5	73.8	66.1	72.4	0.57
6296	114.7	234.2	91.6	114.8	124.3	139.7	136.6	0.05

No one can read this one, too much detail, too small. Cut it down somehow.
George Fritsma, 6/29/2017

Anti-Xa/APTT RESULTS ON LMWH SUBJECTS

GROUPS	Ave: U/ml	Ave: seconds
LMWH 3.8 ND	0.42	37.9
LMWH 3.8 SD	0.37	41.2
LMWH 3.2 ND	0.43	37.1
LMWH 3.2 SD	0.38	39.6
LMWH CTAD ND	0.46	37.7
LMWH CTAD SD	0.43	41.2

Combine this table with the last one, ditch the p value.
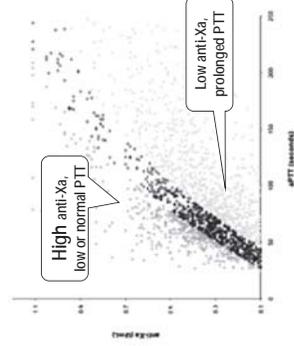George Fritsma, 6/29/2017

Single vs. Hybrid Calibration
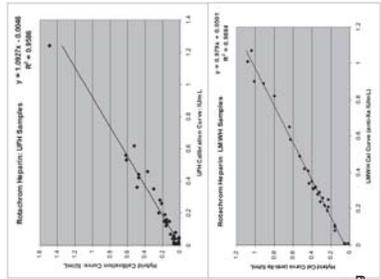
- Anti-Xa methods require calibration
  - UFH & LMWH specific curves
- "Use of a single calibration curve...."
  - Equivalent results obtained
    - UFH vs. hybrid
    - LMWH vs. hybrid

McGlasson DL. Using a single calibration curve with the anti-Xa chromogenic assay for monitoring heparin anticoagulation. Lab Medicine 2005; 36: 297-299

APTT/anti-Xa Discordance

High anti-Xa, low or normal PTT

Low anti-Xa, prolonged PTT

Price EA, Jin J, Nguyen H, et al: Discordant aPTT and anti-Xa values and outcomes in hospitalized patients treated with intravenous unfractionated heparin. Annal Pharmaco. 2013;47:151-8.

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Discordant APTT and Anti-Xa Values

- 42% with anti-Xa in Rx range and PTT above Rx range
- Most were on simultaneous Coumadin
- Elevated risk of major bleed and death

2321 paired values from 539 patients	2 consecutive long PTT versus in-range anti-Xa n = 163	Long PTT versus in-range anti-Xa n = 85	PTT and in-range anti-Xa concordant n=112
Major bleed in 21 d	15 (9%) p = .03	5 (6%)	3 (3%)
2° thrombotic event in 21 d	9 (6%)	3 (4%)	2 (2%)
Death in 30 d	23 (14%) p = .02	18 (21%) p = .0008	6 (5%)

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George Fritsma, 6/20/2017

Ex-vivo method for heparin therapeutic range determination: Marlar 2017

1	**Collect appropriate samples (N=20). Subjects on UFH. CLSI (H21)**
2	**Determine APTT on fresh samples**
3	**Determine heparin level on either fresh or frozen sample**
4	**Plot heparin level on X-axis and APTT on Y-axis**
5	**Determine best fit line using linear regression**
6	**Determine APTT value for both 0.3 U/mL and 0.7 U/mL.**
7	**Heparin therapeutic range is the APTT range between 0.3–0.7 U/mL**
8	**All data and calculations must be available for evaluation**

CONCLUSIONS:

- The anti-Xa heparin results were not statistically affected by any of the collection tubes or blood to anticoagulant ratio.
- Individual APTT results and the anti-Xa assay showed a high degree of discordance. This could lead to inappropriate heparin management.
- In three published studies the rate of discordance was 43-53%. In 86% of those specimens it was caused by a low APTT

CONCLUSIONS:

- The 3.8% citrate collection tube APTT result was affected most by the short draw and anticoagulant effect.
- There was no statistical significant difference between the other collection tubes or anticoagulant ratio on the APTT results. However the results may be skewed.
- The CTAD tube usually yielded the highest amounts of heparin regardless of the anticoagulant.

CONCLUSIONS

- Anti-Xa to reach Rx was 1690 units/hr vs APTT 1884 units /hour. Group managed by anti-Xa testing in range while APTT mean remained subtherapeutic.
- Anti-Xa reached Rx in 16 hrs in 80% or subjects and 87% in 24 hrs. vs 20 hours longer with APTT.
- Cost: 4 day course of UFH with APTT was $27.10 vs $31.46 for anti-Xa. When labor costs factored in for phlebotomy, lab labor, dosing adjustments the cost for anti-Xa testing is cost neutral.

REFERENCES

McGlasson DL. Monitoring Unfractionated Heparin and Low Molecular Weight Heparin Anticoagulation with an anti-Xa Chromogenic Assay using a Single Calibration Curve. Lab Medicine. 2005;36(5):297-299.

McGlasson DL et al: Effects of Pre-analytical Variables on the anti-Fxa Chromogenic Assay when Monitoring Unfractionated Heparin and Molecular Weight Heparin Anticoagulation. Blood Coagulation and Fibrinolysis. 2005;16(3):173-176.

Marlar RA et al: Activated Partial Thromboplastin Time Monitoring of Unfractionated Heparin Therapy Issues and Recommendations. Semin Thromb Hemost 2017;43:253-260.

Vandiver JW. Antifactor Xa Levels vs Activated Partial Thromboplastin Time for Monitoring Unfractionated Heparin. Pharmacotherapy 2012;32(6):546-558.