Measuring Heparin (UFH): APTT, Ratios or Anti-Xa?

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Disclosures (since 2015)

• Honoraria for speaking, advisory meetings for Siemens Healthcare Diagnostics, Boehringer Ingelheim, NovoNordisk, Instrumentation Laboratory
• Expert testimony on Rivaroxaban measurement
• Related to this topic: none
Objectives

• Review clinical indications and considerations for unfractionated heparin (UFH) anticoagulation
• Understand the current laboratory methods and practices used to guide UFH anticoagulation
• Discuss the limitations of these assays and discuss implementation of alternative strategies and hurdles associated with same.
UFH citations


• Laboratory:
UFH: What does it do

- Sulfated glycosaminoglycan which complexes with antithrombin (AT)
  - Kinetically enhances AT activity
  - AT is a serine protease inhibitor
    - Serine proteases:
      - XIIa, XIa, Xa, IXa, Thrombin

- Non-specific UFH binding
  - monocytes, endothelium, circulating proteins
UFH Anticoagulation - Clinical

• Indications
  – Treatment (e.g. VTE, ACS)
  – Prophylaxis (e.g. trauma)
  – Other (e.g. ECLS)

• Infusion dose
  – Weight based (total vs ideal vs adjusted)
  – To bolus or not
  – Maximum infusion rate
UFH Anticoagulation – Clinical

• Weight
• Laboratory Testing – baseline
  – CBC
  – PT and APTT
• Monitoring
  – Infusions vs subcutaneous
  – Guideline driven (e.g. CHEST)
  – Institution specific
  – Others (e.g. JCAHO)
UFH Anticoagulation – Clinical

• Although in place for ~60 years, the supporting evidence for current practices:
  – Weight based: weak
  – Monitoring frequency: weak
  – Monitoring methods (APTT vs anti-Xa): weak
  – Therapeutic targets:
    • APTT: very weak
    • Anti-Xa: very weak

UFH Anticoagulation – Laboratory

- Majority clinical laboratories use APTT
  - Reporting methods
    - Seconds
    - Ratios – historical, not recommended
  - Heparin Therapeutic Range (HTR)
- Alternatives:
  - When baseline APTT is elevated
  - When there is UFH “resistance”
UFH Anticoagulation – Laboratory

• Guidance -US
  – College of American Pathologists (CAP)
    • Checklist requirements
  – Publications
    • CLSI H47-A2 Approved Guideline 2008
    • Described Anti-Xa vs APTT HTR
CAP Recommendations for UFH monitoring

- Baseline aPTT and platelet count
- Therapeutic range for each lot aPTT reagent assessed by ex-vivo samples using:
  - Comparisons with heparin level
    - Anti-Xa or protamine titration
  - Comparisons with previously validated reagents
- Does not advocate in-vitro spiking for determining HTR
Reminder: APTT vs Anti-Xa

**APTT**

- Diagnostic test
  - Factor deficiency
  - Inhibitor assessment
    - Factor
    - Lupus anticoagulant

- Monitoring test
  - UFH
  - DOAC assessment
  - Measure of Rx efficacy
    - FFP/Cryo therapy
    - Factor replacement

**Anti-Xa**

- Monitoring test only
  - UFH
  - LMWH
  - Pentasaccharide
  - DOAC
    - Xarelto (rivaroxaban)
    - Eliquis (apixaban)
    - Saveysa (edoxaban)
Reminder: Limitations of Testing

**APTT**

- **Pre-analytical:**
  - Sample stability, temperature, tourniquet time, site selection, citrate:blood ratio, etc.

- **Analytical:**
  - Factor levels *(high or low)*, inhibitors, anticoagulants, antibiotics, physiology, different lot sensitivity to factors and anticoagulants
  - Not calibrated

**Anti – Xa**

- **Pre-analytical:**
  - Timing of sample
  - Sample stability
  - Site selection
  - Processing

- **Analytical:**
  - Cannot differentiate between anti-Xa drugs
  - Possible challenges with icterus and lipemia
  - Calibrated - Calibration
Revisit: CAP Recommendations for UFH monitoring

• Therapeutic range for each lot aPTT reagent assessed by ex-vivo samples using:
  – Comparisons with heparin level
    • Anti-Xa or protamine titration
  – Comparisons with previously validated reagents

• Does not advocate in-vitro spiking for determining HTR
UFH Therapeutic range

R²: 0.47

70-95 seconds
Heparin Therapeutic Range (HTR)

Brill-Edwards method

- VTE Rx patients only
- Comparison between APTT and Anti-Xa
- APTT HTR corresponding to 0.3 – 0.7 in treated patients

• $R^2$ ranges between 0.35-0.70 (never come close to 0.70)
• Recheck with every APTT reagent lot change
UFH Monitoring: Recommendations

Linearity between APTT and Anti-Xa measurements

Revisit: CAP Recommendations for UFH monitoring

• Therapeutic range for each lot aPTT reagent assessed by ex-vivo samples using:
  – Comparisons with heparin level
    • Anti-Xa or protamine titration
  – Comparisons with previously validated reagents

• Does not advocate in-vitro spiking for determining HTR
Validation of UF heparin sensitivity of aPTT: Comparison with existing, validated reagent

- Accumulating samples and freezing
  - NO minimum number detailed (Brill-Edwards: N=30)
  - Platelet-poor
  - No 2 samples on a given patient
- Select reagent with comparable sensitivity
- Comparison testing
  - old “x” axis vs new “y” axis
- Cumulative summation of differences
  - Mean of new and old reagents
  - Difference between new – old
  - **Cumulative** difference over lots
    - <5sec: NS; 5-7sec: concern; >7sec: action
Evidence supporting CAP summation of differences recommendations for UFH HTR assessment

Concept from S Moll, UNC
Revisit: CAP Recommendations for UFH monitoring

• Therapeutic range for each lot aPTT reagent assessed by ex-vivo samples using:
  – Comparisons with heparin level
    • Anti-Xa or protamine titration
    • Comparisons with previously validated reagents

• Does not advocate in-vitro spiking for determining HTR
In-vitro addition vs Brill-Edwards

UFH Therapeutic range

BE UFH range: 70-95s
In-vitro UFH range: 55-120s
Proposed Alternative HTR Assessment for New lot APTT reagents

* Comparing of commercial or UFH enriched NPP on current and new lot reagents
* Limits: slope? or intercept? or $R^2$? of combination thereof…

Lot 2 = 1.0733$x$ - 4.6963
$R^2 = 0.9965$

Lot 1 = 1.0361$x$ - 0.5173
$R^2 = 0.9984$

New lots SynthasIL

Lot 2 = 0.9107$x$ + 4.3218
$R^2 = 0.99998$

Lot 1 = 1.1709$x$ - 6.0628
$R^2 = 0.9997$

New lots Actin
Heparin Therapeutic Range (HTR)

• Problems for new lot HTR assessment:
  – No recommended sample size
  – No more than 2 samples per patient
  – CAP recommendations (vague)
  – Not reproducible (beginning vs end)
  – Poor sample handling for Anti-Xa testing
  –Occurs every 12-14 mos
  – HTR changes to dosing order sets
UFH Monitoring: Recommendations

Acceptable HTR methods:
• >20 samples (preferred N=30-50)
• <10% from same patient
• Samples with INR <1.3
• Frozen samples acceptable if demonstrated equivalence between fresh and frozen results
• Must be determined on all instruments in use
• Cannot use single instrument for multiple labs/sites/instruments

UFH Monitoring: Why not ratios

UK group\(^1\):
N=30 UFH treated patients with 0.2 – 0.4 U/mL
Ratios varied from 1-6 – 1.9 for least sensitive reagent, but ratios ranging from 2.2 -2 .9 with most sensitive reagent

Canadian group\(^2\):
N=126 UFH treated patients with 0.3 – 0.7 U/mL anti-Xa
Control value = population mean = denominator
Ratios ranged from 1.7 – 6.2

Heparin “resistance”

Failure to achieve a therapeutic aPTT despite adequate or maximal dosing:

- Elevated fibrinogen
- Elevated factor VIII
  - Depressed antithrombin
  - Drug not given
  - Wrong patient collected
Heparin “resistance”

Alternative strategies:
Most likely available, but not often utilized:
Thrombin time
  Linear
  Therapeutic range can be created using UFH enriched normal pooled plasma
May be available:
  Anti-Xa
Different drug: LMWH, pentasaccharide, DTI
Reminder: Anti-Xa activity

plasma [heparin] + (exogenous antithrombin)

Excess fXa

AT-heparin-Xa complex + Residual fXa

Chromogenic substrate

yellow color
Anti-Xa measurements

Two types chromogenic methods:
With or without Antithrombin (AT)

Without AT supplementing
\[ <50\% \text{ AT} = \downarrow\text{Anti-Xa} \]
Sample mixing with NPP

Calibration – variable
UFH, LMWH, Hybrid
Commercial vs In-house preparation
Monitoring UFH with Anti-Xa

Rationale for change – Cost?

• Shorter time to therapeutic target (TTT)
  – Within 6 hours (54% Anti-Xa vs 27% APTT)
  – Within 24 hours (74% Anti-Xa vs 63% APTT)
• Less dosing changes with 24 hours
  – Average 1.7 for APTT
  – Average 1.0 for Anti-Xa

Monitoring UFH with Anti-Xa
Rationale for change – Cost vs Savings?

• TTT
  – Ave 28 Hrs with Anti-Xa vs 48 Hrs with APTT

• More test results within TT goal:
  – 66% for Anti-Xa vs 42% for APTT

• Less rate changes within 24 hours:
  – 0.8 for Anti-Xa vs 1.6 for APTT

Monitoring UFH with Anti-Xa
Rationale for change – Savings?

Less RBC transfusions associated with Anti-Xa UFH monitoring

<table>
<thead>
<tr>
<th>UFH Indication</th>
<th>Bleed % Anti-Xa</th>
<th>Bleed % APTT</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACS</td>
<td>7.0%</td>
<td>24.6%</td>
</tr>
<tr>
<td>Stroke</td>
<td>13.8%</td>
<td>21.9%</td>
</tr>
<tr>
<td>VTE</td>
<td>3.9%</td>
<td>8.6%</td>
</tr>
</tbody>
</table>

Monitoring UFH with Anti-Xa
Rationale for change – ?

• Stanford University hospital
• For ~ 9 years
• Discordant APTT vs Anti-Xa (higher APTT)
  – High 1-2 samples
  – Constant high >2 samples
  – Increased bleeding
  – Increased mortality
• Their practice: first 3 samples APTT + Anti-Xa

## 2016 UCDHS UFH Monitoring

Analyzing the data from UFH treated patients (N=243):

<table>
<thead>
<tr>
<th>Rate Change</th>
<th>Current APTT</th>
<th>Anti-Xa (0.3-0.7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Rate Change</td>
<td>78</td>
<td>143</td>
</tr>
<tr>
<td>Rate reduced</td>
<td>61</td>
<td>53</td>
</tr>
<tr>
<td>Rate increased</td>
<td>78</td>
<td>47*</td>
</tr>
</tbody>
</table>

* Included 15 liver failure patient samples
Reasons (and benefits) to transition for Anti-Xa UFH monitoring

• TTT reached sooner
• Less dose changes
• Less testing
• 24/7 Anti-Xa testing
  – Putative benefit – Anti-Xa DOAC measurements
• No need for annual APTT reagent lot evaluation for HTR (sorta)
  – Never change UFH dosing order sets again (?)
• Dwindling and exiting expertise in the field
• Unlikely cost neutral for the lab sand box
Thank you...

Any Questions?