Advantages of anti-Xa over PTT for heparin monitoring

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• No disclosures.
• Full disclosure is a two-edged sword.
Advantages of anti-Xa over PTT for heparin monitoring

• At UKMC, we decided several years ago to switch from PTT to anti-Xa heparin monitoring.
• In Sept. 2016 we implemented the switch, so we must have had reasons.
• I didn’t originally choose the title for this talk, but I decided to keep it.
• Other possible titles:
  • “Anti-Xa testing may have fewer disadvantages than PTT for heparin monitoring.”
  • “Anti-Xa and PTT: Two methods of heparin monitoring that both have a lot of problems”
Objectives

• Importance of monitoring heparin dosing with laboratory tests.

• Understand basic PTT and anti-Xa methodology.

• Pros and cons of each test for heparin monitoring.
What is heparin?

Natural heparins

- Sulfated glycosaminoglycans – highly charged polysaccharides found in liver, gut, basophils, mast cells
- Probable antibacterial function
- Chemically similar to endothelium-bound *heparans* that bind circulating antithrombin
- All heparins have a common key pentasaccharide sequence – the “business end”
Heparins

- **Unfractionated heparin (UFH):** a mixture of molecular sizes - up to 30 additional sugars
- **Low molecular weight heparin (LMWH, enoxaparin):** only the smaller molecules
- **Fondaparinux:** only the pentasaccharide
Heparin/Antithrombin (AT) System

- Pentasaccharide sequence induces conformational change in AT resulting in ~1000 - 4000 fold increased activity
- Facilitates interaction between AT and thrombin or other proteases in the cascade, esp. FXa
Types of heparin: size matters

- Longer UFH sugar chains can engage both FXa and larger thrombin molecule.
- Shorter LMWH chains cannot engage thrombin, but only FXa; PTT not consistently prolonged.
- PTT is not useful for LMWH monitoring, so anti-Xa is used if monitoring is required.
- Fondaparinux: the business end only.

Source: Am J Health-Syst Pharm © 2002 American Society of Health-System Pharmacists
Pharmaceutical Heparins

- Injectable anticoagulants used to **prevent or treat thrombosis**.
- Can be given subcutaneously 1-3 x/day or by IV injection or infusion at controlled dose and rate.
- **Over- or under-dosing risks bleeding or recurrent thrombosis.** **Narrow therapeutic window**
- Type of heparin, dose, route of administration, and importance of monitoring vary with indication.
Who gets heparin? -Some examples

- Outpatients needing temporary anticoagulation typically get Lovenox® (LMWH) subcutaneously 1-3 x/d, usually without monitoring.
- Perioperative patients often get subcutaneous LMWH or UFH for DVT prophylaxis. LMWH may or may not need monitoring; UFH frequently does.
- Patients with venous thromboembolism usually get UFH by continuous infusion, monitored with PTT or anti-Xa.
- Patients on high dose heparin infusions (e.g., for ECMO) need frequent monitoring, often with POC ACT, and sometimes also with anti-Xa (PICU patients).
How to do PTT

- Test begins with citrated platelet-poor plasma.
- Excess calcium added to neutralize citrate.
- Reagent phospholipid added to fulfill role of removed platelets.
- Clot formation stimulated via “intrinsic pathway” with silica or other surface activator.
- Endpoint is initial detection of clot formation measured in seconds from beginning of test.
PTT reaction starts here on surface of activator, ...

... is affected by activity of “intrinsic pathway” factors, ...

... and stops here.
How to do Anti-Xa

**Anti-Xa activity** performed by adding patient plasma to chromogenic reagent FXa with or without excess of AT. Heparin in specimen interacts with AT to antagonize FXa. Residual FXa activity is inversely proportional to heparin concentration; result calculated using the appropriate calibration curve and expressed in U/mL.
Anti-Xa Monitoring

• More expensive
• Frequent expensive QC
• Technically more difficult and time-consuming
• Reagent stability issues
• Batching once made sense, but now demand is 24/7.
Monitoring heparin
The habits of 40+ years

• PTT has long been familiar to clinicians.
• Cheap, easy to perform, quick turn-around time.
• However, unlike use of PT/INR to monitor warfarin, use of PTT to monitor heparin is not based on large randomized trials showing efficacy and safety.
• The original basis for adopting PTT as standard monitoring for unfractionated heparin (UH) was a 1972 observational study of 234 VTE patients.
• The UFH “therapeutic range” has typically been ~2 x the top of the PTT reference range.
PTT and heparin: multiple problems

Things other than UFH activity can influence PTT.

- Significant diurnal variation of PTT in normal subjects.
- Acute phase reaction - nonspecific heparin adsorption or elevated factor VIII concentration
- Liver disease
- Vitamin K deficiency/VKAs (e.g., warfarin)
- Factor deficiencies and inhibitors
- Lupus anticoagulant
Other PTT/heparin confounders

- Concurrent therapy with warfarin, direct thrombin inhibitors, LMWMH or fondaparinux
- Heparin contamination of the IV line
- Elevated platelet factor 4 in specimen adsorbs heparin; thus platelet count may be important.

- Lupus anticoagulant: a particular problem
- In the presence of LAC, prolonged PTTs do not correlate with adequate anticoagulation.
PTT and heparin: multiple problems

- Patients with prolonged baseline PTT can’t have reliable heparin monitoring using PTT.
- When possible, the cause of the prolonged aPTT should be investigated prior to initiating anticoagulant therapy.
PTT and heparin: it gets worse

• PTT results can’t be considered equivalent to similar results from another laboratory (a problem at UK before we made the switch).
• Degree of PTT prolongation for a given heparin activity varies among different test methods.
• PTTs must be standardized for each laboratory and each lot of reagent.
• This has commonly been done using the factor Xa inhibition assay (anti-Xa).
PTT must be compared to anti-Xa

Both the American College of Chest Physicians (ACCP) and the College of American Pathologists (CAP) recommend that therapeutic ranges of PTT be correlated with UFH activity of 0.3 to 0.7 U/mL by anti-Xa (or 0.2 to 0.4 U/mL by protamine titration assay).

PTT is thus actually a surrogate marker for anti-Xa (albeit a quicker and easier test).
So why not just use anti-Xa?

- Results of anti-Xa assays differ among labs due to various assays used.
- Some assays use separate titration curves for UFH vs. LMWH while other assays use a single hybrid curve.
- Depending on which is used, there may be slight differences in anti-factor Xa activity units reported from different centers.
- Most centers (80 to 90 percent) use assays without added antithrombin (AT): “one-stage assay”.
- Some centers use an assay that adds exogenous AT to potentiate the effect of heparin: “two-stage assay”.
- This can affect results of anti-Xa testing in patients with underlying AT deficiency.
The UK experience
Patient-centered outcomes of the switch

Evaluation of Transition from aPTT to Antifactor Xa Lab Monitoring for Unfractionated Heparin

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UK HealthCare Pharmacy Services, UK HealthCare Gill Heart and Vascular Institute, University of Kentucky College of Pharmacy, UK HealthCare Anticoagulation Stewardship Team
Background and Significance

- Unfractionated heparin (UFH) is an anticoagulant that is utilized for treatment of venous thromboembolism and acute coronary syndrome.
- Laboratory monitoring of UFH is important to optimize its antithrombotic effect and minimize bleeding risk.
- The activated partial thromboplastin time (aPTT) has been traditionally utilized for monitoring UFH primarily because of availability, familiarity, and cost relative to antifactor Xa. However, the aPTT is affected by numerous factors including variation in reagents and analyzers, timing of blood sampling/collection methods, and biological/patient factors.
- Previous studies have demonstrated good correlation exists between antifactor Xa levels and heparin concentrations. Compared to aPTT, antifactor Xa (anti-Xa) monitoring is associated with fewer blood draws and fewer heparin dosing adjustments.
- At UK HealthCare, between UK Good Sam and UK Chandler hospitals, there were n=6 different nurse-managed protocols for adult patients due to differences in lab analyzers which resulted in increased risk of error and monitoring when patients were transferred between facilities.
- In September, 2016, UK HealthCare Hospitals implemented new coagulation analyzers and transitioned to the use of anti-Xa as standard lab monitoring for UFH management.
- For the transition education process, UK Anticoagulation Stewardship Team provided over n=30 live presentations to physicians, nurses, lab personnel, and pharmacists to educate providers about anti-Xa monitoring.

Objectives

Primary outcome:
- The percentage of patients within target range within 24 hours of initiating UFH

Secondary outcomes:
- The percentage of patients within target range within 48 hours of initiating UFH
- Number of infusion rate changes
- Number of lab tests performed
- Number of bleeding or thrombosis incidents during UFH therapy

Methods

- Retrospective chart review, medication utilization evaluation.
- Inclusion criteria: All patients 18 year of age or older who receive UFH infusions at UK Healthcare hospitals from June to August 2016 and October to December 2016.
- Exclusion criteria:
  - UFH duration less than 24 hours or UFH was held for more than 10 hours.
  - UFH was initiated at outside UK Healthcare hospitals.
  - Patients were on ECMO.

Results

Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>aPTT (n=208)</th>
<th>Anti-Xa (n=192)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>60.3 ± 13.4</td>
<td>61.8 ± 13.9</td>
<td>0.259</td>
</tr>
<tr>
<td>Gender, no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>110 (47.1)</td>
<td>80 (41.4)</td>
<td>0.146</td>
</tr>
<tr>
<td>Actual weight mean</td>
<td>89.8 ± 29.4</td>
<td>88.56 ± 24.1</td>
<td>0.652</td>
</tr>
</tbody>
</table>

Table 2. Patient Characteristics

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>aPTT (n=208)</th>
<th>Anti-Xa (n=192)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous PE or DVT</td>
<td>32 (15.4)</td>
<td>28 (14.6)</td>
<td>0.889</td>
</tr>
<tr>
<td>Peripheral-vascular disease</td>
<td>19 (9.1)</td>
<td>16 (8.3)</td>
<td>0.860</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>49 (23.6)</td>
<td>33 (17.2)</td>
<td>0.137</td>
</tr>
<tr>
<td>Chronic kidney diseases</td>
<td>35 (16.6)</td>
<td>28 (14.6)</td>
<td>0.584</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>74 (35.6)</td>
<td>61 (31.8)</td>
<td>0.459</td>
</tr>
<tr>
<td>Diabetes</td>
<td>84 (40.4)</td>
<td>60 (31.3)</td>
<td>0.061</td>
</tr>
<tr>
<td>Hypertension</td>
<td>75 (36.3)</td>
<td>62 (32.3)</td>
<td>0.461</td>
</tr>
<tr>
<td>Heart failure</td>
<td>44 (21.2)</td>
<td>31 (16.1)</td>
<td>0.248</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>124 (59.4)</td>
<td>113 (58.9)</td>
<td>0.919</td>
</tr>
<tr>
<td>Prosthetic heart valve</td>
<td>14 (6.7)</td>
<td>11 (5.7)</td>
<td>0.837</td>
</tr>
<tr>
<td>Liver diseases</td>
<td>6 (2.9)</td>
<td>11 (5.7)</td>
<td>0.215</td>
</tr>
<tr>
<td>Strokes</td>
<td>25 (12.0)</td>
<td>15 (7.8)</td>
<td>0.184</td>
</tr>
<tr>
<td>Cancer</td>
<td>14 (6.7)</td>
<td>11 (5.7)</td>
<td>0.116</td>
</tr>
</tbody>
</table>

Table 3. Other Secondary Outcomes

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>aPTT (n=208)</th>
<th>Anti-Xa (n=192)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of stay, mean (SD)</td>
<td>15.3 (14.9)</td>
<td>13.9 (16.0)</td>
<td>0.363</td>
</tr>
<tr>
<td>Mortality, n (%)</td>
<td>17 (8.2%)</td>
<td>16 (8.3%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Monitoring tests performed (48h, mean (SD))</td>
<td>6.1 (1.8)</td>
<td>5.6 (1.5)</td>
<td>0.004</td>
</tr>
<tr>
<td>Infusion rate changes/48h, mean (SD)</td>
<td>4.4 (2.3)</td>
<td>3.5 (2.1)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Hemoglobin at baseline, mean (SD)</td>
<td>10.7 (2.4)</td>
<td>11.2 (2.5)</td>
<td>0.032</td>
</tr>
<tr>
<td>Lowest hemoglobin while on heparin, mean (SD)</td>
<td>9.6 (2.3)</td>
<td>10.3 (2.3)</td>
<td>0.005</td>
</tr>
<tr>
<td>Platelet at baseline, mean (SD)</td>
<td>210.0 (105.3)</td>
<td>242.7 (193.5)</td>
<td>0.126</td>
</tr>
<tr>
<td>Lowest platelet while on heparin, mean (SD)</td>
<td>190.4 (90.3)</td>
<td>203.3 (95.5)</td>
<td>0.176</td>
</tr>
<tr>
<td>Thrombotic event, n (%)</td>
<td>3 (1.4)</td>
<td>1 (0.5)</td>
<td>0.624</td>
</tr>
<tr>
<td>Bleeding event, n (%)</td>
<td>6 (2.9)</td>
<td>5 (2.6)</td>
<td>1.000</td>
</tr>
<tr>
<td>RBC transfusion, n (%)</td>
<td>1 (0.5)</td>
<td>10 (5.2)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Table 3. Other Secondary Outcomes

Conclusions

Primary outcome:
- Transition to anti-factor Xa monitoring of UFH protocols improved percentage of patients achieving target levels within 24 and 48 hours.
- Live presentations to healthcare providers appeared to be a successful approach to education of the transition process to anti-Xa monitoring.

Secondary outcomes:
- Improved % of patients achieving target levels for Full dose and ACS heparin protocols.
- After transition to anti-Xa monitoring, a decrease in frequency of monitoring required and number of heparin rate changes decreased which could demonstrate decrease in lab cost utilization and nursing time when managing heparin.
- Documented bleeding events remained the same after transition to anti-Xa monitoring but there was an increase in RBC transfusion that requires further evaluation.
- No increase in nursing heparin protocol violations after transition to anti-Xa.

Figure 2. Primary Outcome: Percentage of Patients within Target Range at 24 and 48 hours

Figure 3. Secondary Outcome: Percentage of Patients within Target Range at 24 hours by UFH Heparin

Figure 4. Secondary Outcome: Percentage of Patients Below, Within, or Above Target Range
Major conclusions

• Transition from PTT to anti-Xa for UFH monitoring improved percentage of patients achieving target levels within 24 and 48 hours.
• Following the switch, a decrease in frequency of monitoring and fewer heparin rate changes.
• Documented bleeding events were unchanged, but an increase in RBC transfusion requires further evaluation.
So which test should we use for heparin monitoring?

Few high quality studies comparing PTT vs anti-Xa
Little evidence to support using one over the other (or using both) for routine monitoring
Use whichever test is available.
If both are available, the choice between them (pending further evidence) may be based on cost, convenience, and clinician familiarity.
There may be certain exceptions, such as a baseline prolonged aPTT, and of course LMWH monitoring if indicated.
Thank you

- Questions if time permits ...
- ... or catch me later.