Anticoagulants: New Tools and Old Problems

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Goals and Objectives

• Review the use of anticoagulants encountered in inpatient care
• Review the mechanism of action of anticoagulants and related treatments
• Identify complications of anticoagulant therapy and apply solutions in the hospitalized patient
• Review the newer anticoagulants and their evolving role in patients with clot disease
Case #1

• This is a 61 year-old Hispanic man with a recent diagnosis of testicular cancer, seminoma, stage III B, who was 2 weeks s/p left radical orchiectomy, who now presents to clinic to discuss chemotherapy. He complained of poor appetite, and had not been able to walk for days, due to new leg edema.
Case # 1

- On exam he appears fatigued, has severe temporal wasting and has 3+ bilateral lower extremity pitting edema to include the thighs and lower abdominal wall.
- His labs show:
  - Na 128, BUN 45, Cr 3.26 (baseline 0.98)
  - INR 1.2, PTT 32
- Lower extremity doppler show extensive venous thrombi in the right deep femoral, left femoral, left deep femoral and common femoral veins.
Heparin

• Major anticoagulation action is mediated by the heparin/antithrombin (AT) interaction
• AT is converted from a slow to a rapid inhibitor of coagulation enzymes
• It has a short half-life, is completely reversible, and non-renal elimination
Heparin
Heparin

• Monitoring
  – aPTT
  – Antifactor Xa
  – Protamine titration
Table 1. Preanalytic, Analytic, and Biologic Factors Known to Influence Activated Partial Thromboplastin Time and Antifactor Xa Levels

<table>
<thead>
<tr>
<th>Factor</th>
<th>aPTT</th>
<th>Antifactor Xa</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preanalytic</strong></td>
<td></td>
<td></td>
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<tr>
<td>Blood sampling in the evening (due to diurnal variation)</td>
<td>↑</td>
<td>↔</td>
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<tr>
<td>Blood sampling in the morning (due to diurnal variation)</td>
<td>↓</td>
<td>↔</td>
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<tr>
<td>High concentration of citrate in collection tube (3.2% is standard)</td>
<td>↑</td>
<td>↔</td>
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<tr>
<td>Improper blood sampling (obtaining sample too close to heparin administration site without proper flushing)</td>
<td>↑</td>
<td>↑</td>
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<tr>
<td>Underfilled sample tubes</td>
<td>↑</td>
<td>↔</td>
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<tr>
<td>Delay in sample analysis (&gt; 2 hrs)</td>
<td>↓</td>
<td>↓</td>
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<tr>
<td>Inadequate centrifugation (inadequate removal of platelets from sample)</td>
<td>↓</td>
<td>↓</td>
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<tr>
<td>Gross hemolysis of sample</td>
<td>↔</td>
<td>↓</td>
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<tr>
<td><strong>Analytic</strong></td>
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<tr>
<td>Reagent used (change in lot numbers can also affect results)</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Coagulometer used</td>
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<td>↑</td>
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<tr>
<td><strong>Biologic</strong></td>
<td></td>
<td></td>
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<tr>
<td>Antithrombin deficiency</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Increased levels of acute phase reactants (factor VIII or fibrinogen)</td>
<td>↓</td>
<td>↔</td>
</tr>
<tr>
<td>Increased heparin-binding proteins (inflammation, infection, malignancy)</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Obesity (increased volume of distribution)</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Impaired renal function (decreased UFH elimination)</td>
<td>↑</td>
<td>↔</td>
</tr>
<tr>
<td>Liver disease (decreased clotting factor production)</td>
<td>↑</td>
<td>↔</td>
</tr>
<tr>
<td>Consumptive coagulopathy</td>
<td>↑</td>
<td>↔</td>
</tr>
<tr>
<td>Lupus anticoagulant</td>
<td>↑</td>
<td>↔</td>
</tr>
<tr>
<td>Deficiencies of specific clotting factors (preallikrein and factors IX, XI, and XII)</td>
<td>↑</td>
<td>↔</td>
</tr>
<tr>
<td>Elderly</td>
<td>↑</td>
<td>↔</td>
</tr>
<tr>
<td>Recent use of low-molecular-weight heparins or fondaparinux (particularly in setting of impaired renal function)</td>
<td>↔</td>
<td>↑</td>
</tr>
<tr>
<td>Hypertriglyceridemia (triglyceride level &gt; 360 mg/dl)</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Hyperbilirubinemia (total bilirubin level &gt; 6.6 mg/dl)</td>
<td>↓</td>
<td>↑</td>
</tr>
</tbody>
</table>

*aPTT = activated partial thromboplastin time; ↑ = increase in laboratory result; ↓ = decrease in laboratory result; ↔ = little to no effect; ✸ = variable response; UFH = unfractionated heparin.*
Heparin

• A survey in 2004
  – 97% of institutions were using the aPTT
• Measuring antifactor Xa
  – Fewer laboratory tests
  – Fewer dosage adjustments
  – Counteracts the higher acquisition costs of the antifactor Xa reagents
  – Most coagulometers have the capability to perform colorimetric anifactor Xa testing
  – If total bilirubin is > 6.6 mg/dL, aPTT should be used
Case # 2

• This is a 78 year-old Hispanic man with a history of pleural effusion and suspicious lung mass, who presented with shortness of breath. On exam he appears comfortable, but is tachycardic to 120. O2 sats are 99% on room air. His CXR shows a large right pleural effusion, so he undergoes diagnostics and therapeutic thoracentesis. The effusion is markedly improved and you are awaiting cytology. You become suspicious because his tachycardia does not improve in the following days, so you get a chest CT. A left upper lobe segmental pulmonary embolism is found:
  • CBC shows hgb 12, platelets 180
  • INR 1.0, PTT 43
  • Fluid cytology shows adenocarcinoma, unspecified type
Low Molecular Weight Heparin

• Derived from UFH
• The major anticoagulant effect is by AT-mediated inhibition of coagulation factors
• There is much greater inactivation of Xa than thrombin
• After subcutaneous injection, the bioavailability is as high as 90%
• There is a more predictable anticoagulant response
• Antifactor Xa levels peak 3 to 5 hours after dosing
• Predominantly cleared by the kidney
• Antifactor Xa activity can be checked if needed
Low-Molecular-Weight Heparin versus a Coumarin for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer

• Patients with cancer
• Symptomatic proximal deep vein thrombosis, pulmonary embolism or both
• Randomized to either:
  – LMWH (dalteparin) for 5 to 7 days with coumadin for 6 months with INR goal of 2.5
  – LMWH for 6 months
CLOT

- Dalteparin group
  - 27 of 336 had recurrent thromboembolism (9%)
- Oral Anticoagulant group
  - 53 of 336 had recurrent thromboembolism (17%)
  - No significant difference in major bleeding
  - No significant difference in any bleeding
  - No difference in mortality
3.3.2. In patients with DVT of the leg and cancer, we suggest LMWH over VKA therapy (Grade 2B). In patients with DVT and cancer who are not treated with LMWH, we suggest VKA over dabigatran or rivaroxaban for long-term therapy (Grade 2B).
Case # 3

- This is a 78 year-old Hispanic man with a recent diagnosis of adenocarcinoma (presumed lung) and recent diagnosis of pulmonary embolism.
- He is brought by EMS to the ER with a chief complaint of nausea and large volume hematemesis.
- He is on Lovenox 60 mg SC twice daily, and his last dose was 2 hours ago.
- His pulse is 104, BP 100/50, R 24
- INR is 1.2, aPTT is 28, Hgb is 27
Reversal of LMWH

• No proven method
• Protamine sulfate can neutralize antifactor Xa activity, but it is variable
• Within 8 hours, give protamine sulfate at 1 mg per 100 antifactor Xa units (1mg enoxaparin equals approx 100 anti-Xa units) up to 50 mg. A second dose of 0.5 mg per 100 anti-Xa units should be given if bleeding continues.
• LMWH will inhibit any coagulation of FFP infused (so don’t use it).
Case #4

• This is a 78 year-old Caucasian woman with chronic AFIB who presents with bright red blood per rectum. She has a history of chronic atrial fibrillation and had been on coumadin, but the effect was difficult to control, so about 3 weeks ago she was changed to dabigatran, 160 mg po BID. On presentation she is awake, alert, no acute distress, pale, tachycardic

• Labs: Hgb 5.8, INR 1.2
• EKG: AFIB rate of 98
• Rectal exam shows frankly bloody stool
Dabigatran

- Selective reversible direct thrombin inhibitor
- Given as a prodrug dabigatran etexilate
- Approved for use in the U.S. for non-valvular AFIB at a dose of 150 mg po BID
Dabigatran

- There is no antidote
- Management of life-threatening bleeding
  - Early volume replacement
  - Appropriate RBC transfusion
Case # 5

- This is a 64 year-old Hispanic man s/p mechanical mitral valve replacement who is taking coumadin and falls. He is brought to the EC and found to have a subdural hematoma.
- INR is 3.8
- The effect of coumadin needs to be reversed.
Immediate Reversal of Coumadin

- Fresh Frozen Plasma (FFP) has been the most widely used coagulation factor replacement for urgent reversal of coumadin anticoagulation.
- Given the long half-life of coumadin and the short half-life of coagulants in plasma, Vitamin K must still be given to allow endogenous coagulants to be produced.
Fresh Frozen Plasma

- Severe allergic reactions
- Transfusion associated circulatory overload (TACO)
- Transfusion-related acute lung injury (TRALI)
- Potential carrier of infective agents
- Takes time to thaw
- Must be cross-matched if group specific plasma is to be used
TRALI

- Risk is greater than transmission of Hepatitis C and HIV
- Significant morbidity and mortality
- Most frequent cause of transfusion-related death
TRALI

- Acute hypoxemia
- Non-cardiogenic pulmonary edema
- During or after transfusion
- Mirrors ARDS
- Reported in all types of blood components
  - FFP is the most frequently implicated
  - Antibodies to leukocytes implicated in 65-90%
  - More common in female donors with history if pregnancy
Prothrombin Complex Concentrates

- More effective in correcting the INR
- Do not require cross-match
- Virally inactivated
- Can be infused in 15 to 30 minutes
- Do not pose risk for volume overload
Prothrombin Complex Concentrates

• Three factor products
  – II, IX, X (low in factor VII)
  – Profilnine

• Four factor products
  – II, VII, IX, X (also factor II, C & S)
  – Kcentra, recently approved in US for emergent reversal of Vitamin K antagonists
Recombinant activated factor VII

• Can generate a thrombin burst with both tissue factor dependent and tissue factor independent mechanisms
• Even with platelet dysfunction
• Potential for thrombotic events
• Recommended only for life-threatening bleeds and when other agents (i.e. PCC) are not available.
Case # 6

- The patient has daily ECHO without anticoagulation for 10 days, and heparin is started on day 11. Day 13 the patient develops new headache. Head CT shows a new subdural hematoma.
Protamine

- Protamine sulfate rapidly reverses the anticoagulation effect of heparin
- A basic protein derived from fish sperm
- Binds to heparin to form a stable salt
- aPTT can be used to assess effectiveness
Case # 7

- This is a 78 year-old Caucasian woman with chronic AFIB who presents with bright red blood per rectum. She has a history of chronic atrial fibrillation and had been on coumadin, but the effect was difficult to control, so about 3 weeks ago she was changed to rivaroxaban, 20 mg po every evening. On presentation she as awake, alert, no acute distress, pale, tachycardic
- Labs: Hgb 5.8, INR 1.2
- EKG: AFIB rate of 98
- Rectal exam shows frankly bloody stool
Rivaroxaban

• A direct inhibitor of factor Xa
• Inhibition of factor Xa is highly dependent on drug concentration
• Induces prolongation of the PT, aPTT and other tests
Rivaroxaban

• Reversal
  – Perzborn et al
  – 2009
  – Studied the effect of PCC in rats given high dose IV rivaroxaban
  – Prolongation in the bleeding time was stopped at higher doses
Rivaroxaban

- Reversal
  - Recent studies using 2 different PCCs in healthy volunteers who had been given rivaroxaban
  - Both were equally effective in promoting thrombin generation, enough to overcome the effects of rivaroxaban
  - This study is far from clinical conditions one might encounter in a bleeding patient on rivaroxaban
  - A randomized controlled trial is felt to be unlikely, as patients on rivaroxaban with severe enough bleeding to merit PCC is a small and heterogeneous population
  - Discontinuation of the drug and supportive transfusion may be a more commonly acceptable strategy
Case # 8

• This is a 52 year-old Caucasian woman brought to the ER after falling from standing and hitting the floor hard. She is found to have a subdural hematoma. During her laboratory screening she was found to have a PT of 50 and an aPTT 190. Further history indicated she had undergone knee surgery 6 months ago without any pre-surgery clotting tests, and had no (bleeding) complications.
Mixing Study

• You need to know whether this is a coagulation factor deficiency or an inhibitor
• In a mixing study, the patients plasma is mixed in a 1:1 ratio with normal pooled plasma.
• Then the abnormal coagulation studies are repeated
Mixing Study

- If the clotting tests normalize, a factor deficiency was the cause of the test.
- If the coagulation tests remain abnormal after the 1:1 dilution, an inhibitor is present.
- An inhibitor is much more common than factor deficiency in patients not on anticoagulant therapy.
Case # 8

• This patient made a rapid recovery and had complete resolution of the subdural hematoma without rebleeding and without treatment
Case # 8

- The inhibitor was discovered to be an antithrombin IgA paraprotein
- This antibody has been synthesized and is in extensive pre-clinical testing.
- It is thought to work by binding to and inactivating exosite 1, the part of the thrombin molecule that cleaves fibrinogen into fibrin
- And, most curiously, clot that occurs at vascular tears or cuts is unaffected, intraluminal clot formation is inhibited
Ichorcumab

• This novel anticoagulant, could be the next generation anticoagulant that leaves good clot alone and prevents bad clot from forming.
• Named after “Ichor” the Greek Mythological “blood of the gods” that made them immortal
Reference List


