Stop the Bleeding – An Update on Hemophilia Treatment

Event Type
Live Online

ACPE Expiration Date
12/12/2016

Credits
1 Contact Hour

Target Audience
Nurses, Pharmacists, Pharmacy Technicians

Program Overview
Pharmacists can play a pro-active role in the treatment of hemophilia but must understand the disease and the latest advances in pharmacotherapy. Pharmacists are often the medical professional that patients reach out to for the latest in drug information. This continuing education course gives the pharmacist a solid knowledge base to enlighten the patients on therapies with an emphasis on the need for medication adherence, counseling, drug contraindications, and general safety issues.

Nurse Educational Objectives
- Describe the etiology and epidemiology of hemophilia to include the indications for prophylaxis in the management of hemophilia
- Review the current and emerging pharmacological approaches to the management of hemophilia (pharmacologic profiles, efficacy, side effects, and adverse events)

Pharmacist Educational Objectives
- Describe the etiology and epidemiology of hemophilia to include the indications for prophylaxis in the management of hemophilia
- Review the current and emerging pharmacological approaches to the management of hemophilia (pharmacologic profiles, efficacy, side effects, and adverse events)
- Describe the role pharmacists can play in counseling hemophiliac patients on lifestyle changes, drug treatment strategies and medication adherence to improve quality of life

Pharmacy Technician Educational Objectives
- List the signs and symptoms of hemophilia
- List medications used to treat hemophilia
Activity Type
Knowledge

Accreditation
Nurse N-861
Pharmacist 0798-0000-13-254-L01-P
Pharmacy Technician 0798-0000-13-254-L01-T

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Assistant Professor, University of Maryland School of Pharmacy

Financial Support Received From
Baxter

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Objectives

- Describe the etiology and epidemiology of hemophilia to include the indications for prophylaxis in the management of hemophilia.
- Review the current and emerging pharmacological approaches to the management of hemophilia (pharmacologic profiles, efficacy, side effects and adverse events).

Objectives

- Describe the role that pharmacists can play in counseling hemophiliac patients on lifestyle changes, drug treatment strategies, and medication adherence to improve quality of life.
Hemophilia

• X-linked congenital heterogenous deficiency in a plasma coagulation protein due to a mutation
• Hemophilia A (classic)
  • Deficiency in Factor VIII
• Hemophilia B (Christmas disease)
  • Deficiency in Factor IX

Hemophilia Epidemiology

• Estimated frequency of approximately one in 10,000 births
• 400,000 people in the world
• Hemophilia A more common (80-85%)
• More common in males on the maternal side

Diagnosis

• Consider in any male with unusual bleeding
• Family history
• (+) hemophiliac
  • Test brother(s) for hemophilia
  • Test sister(s) for carrier status
• Prenatal testing
Lab Abnormalities

- Prolonged aPTT
- Decreased factor VIII or factor IX level
- Normal PT
- Normal platelet count
- Normal von Willebrand factor
- Normal bleeding time
- Bethesda titer — abnormal if inhibitor +

aPTT = activated partial thromboplastin time; PT = prothrombin time

Hemophilia Classification

<table>
<thead>
<tr>
<th>Classification</th>
<th>Factor concentration</th>
<th>Clinical Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>&gt; 0.05 – 0.4 Units/mL (&gt;5 – 40%)</td>
<td>Hemorrhage with major trauma or surgery; May go years without diagnosis</td>
</tr>
<tr>
<td>Moderate</td>
<td>0.01 – 0.05 Units/mL (1 – 5%)</td>
<td>Occasional spontaneous hemorrhages; Hemorrhage with mild trauma/surgery that is prolonged</td>
</tr>
<tr>
<td>Severe</td>
<td>&lt; 0.01 Units/mL (&lt;1%)</td>
<td>Frequent spontaneous hemorrhages; Life-threatening hemorrhages</td>
</tr>
</tbody>
</table>

Normal plasma range = 0.5 – 1.5 units/mL

Patient Case

- JM is a 23 year old man with diagnosis of hemophilia, weighing 143 pounds, injures himself after falling off of his bike. He is brought to the hospital for further management.
- PMH: easy bruising and progressively worsening arthritis (knee joints)
- FH: brother deceased (intracranial hemorrhage at 1 year old)

JM’s Laboratory Findings

<table>
<thead>
<tr>
<th>Coagulation Test</th>
<th>Lab Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet (cells/μL)</td>
<td>280,000</td>
</tr>
<tr>
<td>Bleeding time</td>
<td>6 minutes</td>
</tr>
<tr>
<td>Prothrombin time (PT)</td>
<td>11 seconds</td>
</tr>
<tr>
<td>Activated partial thromboplastin time (aPTT)</td>
<td>58 seconds</td>
</tr>
<tr>
<td>Factor VIII (units/mL)</td>
<td>0.005</td>
</tr>
<tr>
<td>Factor IX (units/mL)</td>
<td>1.0</td>
</tr>
</tbody>
</table>
Management of Hemophilia

Goals of Therapy

- Promote adequate hemostasis with minimal side effects with deficient clotting factor
- Prevent transmission of viral and “other” pathogens
- Promote hemostasis in the presence of inhibitors (and minimize inhibitor formation?)
- Cost and ease of use

Preventative Therapy

- Hepatitis A and B immunizations
- Surgery → Maintain factor levels of at least 0.5-0.7 units/mL (50-70%)
- Prompt self treatment
- Home treatment → decreased pain, dysfunction, and long-term disability
- Injury avoidance

Preventative/Supportive Therapy

- Swelling
- Infection
- Dental hygiene
- Pain management
  - Acute pain → bleeding
  - Chronic pain → joint damage from hemarthrosis
- Consider corticosteroids, acetaminophen, narcotics

Factor VIII and IX Concentrates

- Plasma-derived factors
  - Blood donations → risk of infection
- Recombinant factors
  - Effective as plasma derived factors
  - First-line therapy
  - Low risk of infection transmission
  - Development of an inhibitory antibody ~28-33%


Guidelines for Factor Replacement

<table>
<thead>
<tr>
<th>Hemorrhage</th>
<th>Factor VIII (% of normal)</th>
<th>Factor IX (% of normal)</th>
<th>Duration (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe</td>
<td>60 – 100</td>
<td>50 – 100</td>
<td>10 – 14</td>
</tr>
<tr>
<td>Intra-cranial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retro-peritoneal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retro-pharyngeal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>30 – 60</td>
<td>25 – 50</td>
<td>3 – 7</td>
</tr>
<tr>
<td>Hemarthroses</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematuria</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor</td>
<td>20 – 40</td>
<td>15 – 30</td>
<td>1 – 3</td>
</tr>
<tr>
<td>Epistaxis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral (mild)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>50 – 100</td>
<td>50 – 100</td>
<td>Up to 14</td>
</tr>
</tbody>
</table>

Dosing of Recombinant Factors

<table>
<thead>
<tr>
<th></th>
<th>Factor VIII</th>
<th>Factor IX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial Dose (units)</td>
<td>Desired increase (%) x Weight (kg) x 0.5</td>
<td>Pediatric: Desired increase (%) x Weight (kg) x 1.4 Adult: Desired increase (%) x Weight (kg) x 1.2</td>
</tr>
<tr>
<td>Maintenance Dose (units)</td>
<td>50% of initial dose</td>
<td>50% of initial dose</td>
</tr>
<tr>
<td>Expected Response</td>
<td>1 Unit/kg = ↑ by 2% (0.02 Units/mL)</td>
<td>1 Unit/kg = ↑ by 1% (0.01 Units/mL)</td>
</tr>
<tr>
<td>Half-life (hours)</td>
<td>8 – 15</td>
<td>11 – 27</td>
</tr>
<tr>
<td>Dosing interval</td>
<td>12 – 24 (minor bleed) 8 – 12 (moderate – severe bleed)</td>
<td>12 – 24</td>
</tr>
</tbody>
</table>

Hemophilia A Treatment Options

- Advate® (Baxter) – 3rd generation
- Helixate FS® (Bayer) – 2nd generation
- Kogenate FS® (Bayer) – 2nd generation
- Recombinate® (Baxter) – 1st generation
- Xynta® (Pfizer) – 3rd generation

- Hemofil M® (Baxter)²
- Hemofil M® with nanofiltration (Baxter)²
- Monoclate P®
- Koate-DVI® (Grifols)

- Alphanate® (Grifols)
- Humate-P® (CSL Behring)

- Also contains von Willebrand Factor
- Derived from human plasma
- Formulation expires January 2016
- New formulation September 2013
**Hemophilia B Treatment Options**

<table>
<thead>
<tr>
<th>Recombinant Factor IX Concentrates</th>
<th>Human Plasma-derived Factor VIII Concentrates</th>
<th>Plasma-derived Intermediate Purity Concentrates*</th>
</tr>
</thead>
<tbody>
<tr>
<td>BeneFIX® (Pfizer)</td>
<td>AlphaNine SD® (Grifols)</td>
<td>Alphanate® (Grifols)</td>
</tr>
<tr>
<td>Rixubis® (Baxter)</td>
<td>Mononine® (CSL Behring)</td>
<td>Humate-P® (CSL Behring)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Koate-DVI® (Grifols)</td>
</tr>
</tbody>
</table>

* Also contains von Willebrand Factor

**Factor Concentrates: Monitoring**

- **Efficacy**
  - Plasma factor levels
  - Inhibitor levels
  - Control of bleeding
- **Safety**
  - Hypotension
  - Injection site reaction/pain
  - Dyspnea
  - Hypersensitivity
  - Thrombosis (Factor IX)

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**JM's Treatment**

- Upon admission, JM is found to have a retroperitoneal bleed due to his fall from his bicycle. His weight is 143 lbs. His factor VIII level is 0.5%

Calculation: using 100% as desired target
- Dose = (Desired increase)(weight)(0.5)
- Dose = (100% - 0.5%)(65)(0.5)
- Dose = 3233 units

**Desmopressin**

- Vasopressin synthetic analog
- Causes release of von Willebrand factor and factor VIII
- Treatment of mild or moderate hemophilia A
  - Higher baseline level (0.1 – 0.15 Units/mL) → better response
  - Avoid if factor VIII level ≤ 5% or moderate to severe renal impairment

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**References**

Desmopressin

- **Dosing:**
  - IV: 0.3 mcg/kg in 50 mL of NS (15 – 30 mins)
  - Intranasal (Stimate®): 150 – 300 mcg per dose
- Can be given daily for 2 – 3 days
  - Tachyphylaxis with repeated dosing
  - 30% lower response with second dose
- Response rate = 80 – 90%

NS, normal saline; IV, intravenous

Desmopressin Side Effects

- Facial flushing
- Headaches
- ↑ heart rate/↓ blood pressure
- Thrombosis
- Water retention
- Hyponatremia (low sodium)

Antifibrinolytic Therapy

- **Adjunctive therapy** – inhibits clot lysis
- **Oral bleeding** → fibrinolytic enzymes (saliva)
- Aminocaproic acid (oral or IV)
  - 100 mg/kg (max 6 grams) every 6 hours
- Tranexamic acid
  - 25 mg/kg (max 1.5 grams) PO every 8 hours
  - 10 mg/kg (max 1 gram) IV every 8 hours

IV, intravenous; PO, oral

Antifibrinolytic Therapy Side Effects

- Thrombosis
- Headache/migraine
- Renal failure
- Hypotension
- Rhabdomyolysis (aminocaproic acid)
- Visual disturbances (tranexamic acid)
- Anaphylaxis (tranexamic acid)
Fresh Frozen Plasma (FFP) and Cryoprecipitate

- FFP contains all coagulation factors
- Cryoprecipitate contains significant quantities of FVIII, von Willebrand factor, fibrinogen and FXIII
- Not recommended routinely due to concerns about safety and quality

Prothrombin Complex Concentrates (PCCs)

- Treatment of Hemophilia B
- Contain non-activated factors II, VII, IX, and X
- Activated PCCs (aPCCs) contain greater quantities of the activated factors
- Dose and duration – follow guidelines for Factor IX replacement

Adverse Effects

- Thrombotic complications
- Dizziness
- Nausea
- Hives
- Flushing
- Headaches
- Allergic reaction

Prophylactic Replacement

- Recurrent joint bleed → severe physical disability
- Goal: prevent bleeding and joint destruction by preserving normal musculoskeletal function
- Maintain at minimum of 0.01 units/mL (1%)
- Unclear if all patients should continue into adulthood
Prophylactic Factor Replacement

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Episodic treatment</td>
<td>Treatment given at time of clinically relevant bleeding</td>
</tr>
<tr>
<td>Continuous Prophylaxis</td>
<td></td>
</tr>
<tr>
<td>Primary Prophylaxis</td>
<td>Regular continuous treatment in the absence of documented osteochondral joint disease and started before second clinical evident large joint bleed and age 3 years</td>
</tr>
<tr>
<td>Secondary Prophylaxis</td>
<td>Regular continuous treatment after 2 or more bleeds into large joints and before onset of joint disease</td>
</tr>
<tr>
<td>Tertiary Prophylaxis</td>
<td>Regular continuous treatment started after onset of joint disease</td>
</tr>
<tr>
<td>Intermittent Prophylaxis</td>
<td>Treatment given to prevent bleeding for periods not exceeding 45 weeks in a year</td>
</tr>
</tbody>
</table>

Inhibitory Antibodies

Presence of Inhibitory Antibodies

- Serious complication
- More common in severe hemophilia
- Lower incidence in hemophilia B
- Suspected with decreased clinical response to factor replacement

Prothrombin Complex Concentrates (PCCs)

- Treatment of inhibitors

<table>
<thead>
<tr>
<th>Concentrate</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoplex-T</td>
<td>25 – 100 Units/kg, repeat PRN</td>
</tr>
<tr>
<td>FEIBA-VH</td>
<td>Mucous: 50 – 100 Units/kg every 8 hours</td>
</tr>
<tr>
<td></td>
<td>Soft tissue: 100 Units/kg every 12 hours</td>
</tr>
<tr>
<td></td>
<td>Severe: 100 Units/kg, every 12 hours</td>
</tr>
<tr>
<td>Konyne-80</td>
<td>75 Units/kg every 12 hours</td>
</tr>
<tr>
<td>Proplex-T</td>
<td>75 Units/kg, repeat PRN</td>
</tr>
</tbody>
</table>

Recombinant Factor VIIa (NovoSeven RT®)

- Active only at site of tissue injury
- Prevention and treatment of bleeding
- Dose = 90 – 120 mcg/kg
- Short half-life → redose every 2 hours
  - Continuous infusion
- No laboratory test available
- Adverse event: thrombosis (low risk)

Porcine Factor VIII

- Alternative in hemophilia A + inhibitors
- Cross-reactivity
- Severe allergic reactions
- Thrombocytopenia
- Indications
  - No response to Factor VIIa and PCC
  - Patients with severe hemorrhages

Inhibitor Eradication

- Immune tolerance therapy
  - Dosing ranging from 25 Units/kg every other day to 200 Units/kg daily
- Cyclophosphamide
- Prednisone
- IVIG
- Rituximab
  - Rapid depletion of circulating B cells

Consequences of Hemophilia

- Musculoskeletal problems
- Severe, debilitating chronic joint disease
- Diseases transmitted through blood products
- Large demands on health care resources

Comprehensive Care

- Promote physical and psychosocial health and quality of life
- Carry easily accessible identification indicating diagnosis and type of factor needed for repletion
- Multidisciplinary care team needed to address prevention and treatment
- Vein care
- Dental care

Pharmacy Considerations

- Medication regimen review
  - Avoid NSAIDs, aspirin, and drugs affecting platelet adhesion
- Evaluation of factor concentrate dosing regimens for treatment and prophylaxis
- Insurance authorizations
- Communicate with hemophilia comprehensive care team

Conclusions

- Hemophilia is a genetic bleeding disorder more commonly observed in males
- Factor replacement is recommended if available
- Prophylaxis should be considered in all hemophilic patients
- Adjunct therapy requires education for compliance