Faculty Disclosure

RONALD A SACHER, MD, FRCPC FCAP

- On the speakers bureau of BAYER BIOLOGICALS (also a consultant);
- GLAXO SMITH KLINE AND ORTHO BIOTECH.
Faculty Disclosure

Ronald A. Sacher, MD, FRCPC, FCAP

- Dr. Sacher has no financial interests/relationships with Novo-Nordisk but will mention non–FDA approved (off-label) uses of Novo-seven.
Agenda

<table>
<thead>
<tr>
<th>Topic: CP104 Transfusion Medicine College</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>How much RhIg is enough?</td>
<td>8:30-9:00</td>
</tr>
<tr>
<td>Plasma: Liquid Gold or Fool’s Gold?</td>
<td>9:00-9:30</td>
</tr>
<tr>
<td>rVIIa: Universal hemo$ta$i$?</td>
<td>9:30-10:00</td>
</tr>
<tr>
<td>Thanksgiving Break</td>
<td>10:00-10:30</td>
</tr>
<tr>
<td>Transfusion committee revitalization:</td>
<td>10:30-11:00</td>
</tr>
<tr>
<td>making audits work</td>
<td></td>
</tr>
<tr>
<td>Beyond Accreditation: Knowing-and Telling- that you’re doing a good job</td>
<td>11:30-12:00</td>
</tr>
<tr>
<td>Holiday Break (Lunch)</td>
<td>12:00-1:30</td>
</tr>
</tbody>
</table>
Agenda

<table>
<thead>
<tr>
<th>Topic</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topic: CP104 Transfusion Medicine College</td>
<td></td>
</tr>
<tr>
<td>Making a living in Transfusion Medicine in a community hospital</td>
<td>1:30-2:00</td>
</tr>
<tr>
<td>When blood is not available!</td>
<td>2:00-2:30</td>
</tr>
<tr>
<td>My patient refuses blood!</td>
<td>2:30-3:00</td>
</tr>
<tr>
<td>Spring Break</td>
<td>3:00-3:30</td>
</tr>
<tr>
<td>So now you tell me! Managing recalls and Market withdrawals</td>
<td>3:30-4:00</td>
</tr>
<tr>
<td>T&amp;S and the Three Day Rule-Does it make sense in today’s market?</td>
<td>4:00-4:30</td>
</tr>
<tr>
<td>JUST DO IT!: Diagnosis and management of acute transfusion reactions</td>
<td>4:30-5:00</td>
</tr>
<tr>
<td>Commencement</td>
<td></td>
</tr>
</tbody>
</table>
UHC: rVII APPLICATIONS

RONALD A. SACHER MD
PROFESSOR OF INTERNAL MEDICINE AND PATHOLOGY
DIRECTOR OF HOXWORTH BLOOD CENTER
UNIVERSITY OF CINCINNATI MEDICAL CENTER

- NORMAL HEMOSTASIS
- ABNORMAL HEMOSTASIS
- INDICATIONS FOR r VII THERAPY
- OFF- LABEL

© College of American Pathologists 2004. Materials are used with the permission of Ronald A. Sacher, MD, FCAP.
Novoseven
UNIVERSAL HEMOSTATIC/WONDER DRUG ???

- WALL STREET JOURNAL March 17, 2004
- Sales have increased 10 fold since 1997
- Mostly for off-label use
  - To staunch severe bleeding from car accidents, gunshot wounds and post-operative hemorrhage
  - Cost of one dose…. $5,000.00
  - Usual dose is 90 u/kg q 2 hourly (if bleeding continues and if there was a response after first dose)
NORMAL HEMOSTASIS

- HEMOSTASIS IS THE GOAL OF A DELICATELY BALANCED BIOCHEMICAL SYSTEM
- IMBALANCE CAN LEAD TO HEMORRHAGIC OR THROMBOTIC PHENOMENA
- APPRECIATION OF THE COAGULATION PATHWAY IS NECESSARY IN THE INVESTIGATION AND MANAGEMENT OF HEMORRHAGIC PROBLEMS
Hemostasis

Subendothelial matrix

Hemostatic plug

Endothelial cell

WBC

Platelets

Fibrin

RBC

WBC
NORMAL HEMOSTASIS

• First step in hemostasis is formation of a platelet aggregate
• At the molecular level interaction of coagulation factors takes place on the surface of activated platelets
• The Tissue Factor–FVIIa complex is the physiological activator of normal hemostasis
Resting platelet GP IIb/IIIa receptors in unreceptive state

Agonist
ADP, thrombin, collagen

Fibrinogen

Inhibition of platelet aggregation
GP IIb/IIIa receptors occupied by antagonists

Aggregating platelets

GP IIb/IIIa antagonist
rVIIa: mechanism of action

- Tissue Factor
- rFVIIa

- Factor X
- Factor Xa

- Prothrombin (II)
- Thrombin (IIa)

- Fibrinogen
- Fibrin

- F:XIIIa
- Clot
Recombinant Factor VIIa (rFVIIa) in high concentration binds to platelets; this complex catalysis further coagulation. The local coagulation activation is greatly enhanced.
Initiation of coagulation

Xa Generation on Lipid Surface by TF:VIIa
FVIIa Binding to Platelets

HEMORRHAGIC DISORDERS PATHOGENESIS

- FAILURE OF PRIMARY HEMOSTASIS
  - PLATELET/VESSEL WALL INTERACTION
- FAILURE OF SECONDARY HEMOSTASIS
  - FORMATION OF STABLE FIBRIN
- UNIMPEDED ACTION OF FIBRINOLYTIC PATHWAY
HEMORRHAGIC DISORDERS
PLATELET BLEEDING DISORDERS

- QUANTITATIVE/THROMBOCYTOPENIA
- CAUSES OF THROMBOCYTOPENIA
  - IMPAIRED PRODUCTION
  - DISORDERED DISTRIBUTION
  - DILUTION
  - DESTRUCTION
    - IMMUNE
    - NON-IMMUNE
      - DIC, MICRO-ANGIOPATHIC HEMOLYTIC ANEMIA
      - THROMBOTIC THROMBOCYTOPENIC PURPURA
HEMORRHAGIC DISORDERS
PLATELET BLEEDING DISORDERS

● QUALITATIVE/THROMBOPATHIA
  ▪ INHERITED
    ▪ eg. VON WILLEBRAND DISEASE
  ▪ ACQUIRED
    ▪ eg UREMIA
    ▪ DRUGS
    ▪ DYSPROTEINEMIAS
    ▪ DIC
    ▪ MYELOPROLIFERATIVE DISORDERS
PLATELET INHIBITORS

- ASA
- Clopidogrel (Plavix), Ticlid
- Aggrastat (tirofiban)
- ReoPro (abciximab)
- Integrilin (eptifibatide)
HEMORRHAGIC DISORDERS
COAGULOPATHIES

- **INHERITED**
  - HEMOPHILIAS
  - VON WILLEBRAND’S DISEASE

- **ACQUIRED**
  - DISSEMINATED INTRAVASCULAR COAGULATION
  - LIVER DISEASE
  - DEFICIENCY OF VITAMIN K DEPENDANT FACTORS
  - WARFARIN OVERDOSE
  - INHIBITORS OF COAGULATION
HEMORRHAGIC DISORDERS PATHOGENESIS

- **PATIENTS WITH COAGULATION INHIBITORS**
- **ANTIBODIES TO COAGULATION PROTEINS**
  - **SPECIFIC**
    - Anti Factor VIII /IX /OTHERS
      - ALLO-ANTIBODIES
        - HEMOPHILIA (15%)
      - AUTO-ANTIBODIES
        - SPONTANEOUS (POST-PARTUM/ELDERLY/SLE/CLL)
  - **NON-SPECIFIC**
    - PARAPROTEINEMIAS
    - DYSPROTEINEMIAS
HEMORRHAGIC DISORDERS
UREMIA

PATHOGENESIS
- PLATELET DYSFUNCTION
  - CALCIUM/PROSTAGLANDIN/ADHESION DEFECTS
  - ANEMIA MAY DECREASE MARGINATION

MANAGEMENT
- DEFECT MAY BE CORRECTED BY DIALYSIS
- CORRECTION OF ANEMIA(EPO OR ACUTELY BY TX-IDEALLY TO AN HEMATOCRIT OF > 30%
- PLATELET TX GENERALLY INEFFECTIVE
- CRYOPRECIPITATE INFUSION (EFFECT LASTS 24 HRS)
- DESMOPRESSIN (DDAVP)
  MAXIMUM EFFECT WITHIN 4 HRS
  EFFECT DIMINISHES WITH REPEATED INFUSIONS
HEMORRHAGIC DISORDERS
HEPATIC FAILURE

**PATHOGENESIS**
- DECREASED SYNTHESIS OF COAGULATION FACTORS
- DYSFUNCTIONAL FIBRINOGEN SYNTHESIS
- DISSEMINATED INTRAVASCULAR COAGULATION
  - REDUCED CLEARANCE OF ACTIVATED COAGULATION FACTORS
- DEFICIENCY OF ANTITHROMBIN
- THROMBOCYTOPENIA
- SPECIFIC COMPLICATIONS IN PORTAL HYPERTENSION
  - IMPAIRED PRIMARY HEMOSTASIS/VASCULAR FRAGILITY
- COMPLICATIONS OF MASSIVE TRANSFUSIONS
- FIBRINOLYSIS
  - DECREASED CLEARANCE OF ACTIVATED PROTEOLYTIC ENZYMES (eg tPA)
HEMORRHAGIC DISORDERS
DRUG INDUCED COAGULOPATHY

- **WARFARIN**
  - Immediate reversal in hemorrhagic crises
    - FRESH FROZEN PLASMA
      - 15 ML/Kg OR 4-5 UNITS PER ADULT
    - VITAMIN K ADMINISTRATION
      - 10 MG IVI/SQ OTHERWISE 2-10 mg
    - ORAL VIT K (1 mg) LOWERS THE INR MORE RAPIDLY THAN
      SUB Q IN ASYMPTOMATIC PATIENTS(INR 4.5-10)
  
  *ANN INTERN MED 2002 137:251-254*

- **HEPARIN**
  - 25-50 mg PROTAMINE AS GUIDED BY THE ACT OR PTT

- **DIRECT THROMBIN INHIBITORS**
  - R-HIRUDIN, ARGATROBAN, BIVALIRUDIN
  - NO ANTIDOTE/ RENAL FILTRATION OR HEPATIC CLEARANCE
HEMORRHAGIC DISORDERS
DISSEMINATED INTRAVASCULAR COAGULOPATHY

- PATHOGENESIS
  - END POINT OF MANY DIFFERENT STIMULI
  - INTRAVASCULAR THROMBIN GENERATION

- MANAGEMENT
  - TREATMENT OF THE CAUSE
  - REPLACEMENT OF BLOOD COMPONENTS
    - PLATELETS >50,000 (SURGICAL SETTING)
    - FIBRINOGEN >100 mg/dL (10-15 u of cryoprecipitate)
  - USE OF INHIBITORS
    - ACTIVATED PROTEIN C (APC)
    - ANTITHROMBIN
HEMORRHAGIC DISORDERS
MANAGEMENT IN TRAUMA

- SPECIFIC ISSUES: MASSIVE BLEEDING
  - COMPLEX/ MULTIFACTORIAL
  - COMPLICATING FACTORS
    - HYPOTHERMIA
    - DILUTIONAL COAGULOPATHY/THROMBOCYTOPENIA
    - FUNCTIONAL COAGULOPATHIES
      - HEPATIC DYSFUNCTION / SHOCKED LIVER
      - DISSEMINATED INTRAVASCULAR COAGULOPATHY
HEMORRHAGIC DISORDERS
RECOMBINANT FACTOR VIIa

- SUCCESS USING PLASMA DERIVED FACTOR VIIa PROMPTED DEVELOPMENT OF THE RECOMBINANT PRODUCT
- DATA SUGGEST THAT rVIIa ACTS PREFERENTIALLY AT THE SITE OF INJURY THUS THROMBOEMBOLIC RISK LOW
- MAY BE USEFUL IN HEMORRHAGIC LIVER DISEASE
  - SUCCESSFULLY USED IN LIVER TRANSPLANTATION
HEMORRHAGIC DISORDERS
RECOMBINANT FACTOR VIIa

- LABELLED INDICATION:
- TREATMENT OF BLEEDING IN PATIENTS WITH HEMOPHILIA A or B WITH INHIBITORS
- MARKETING APPROVAL OBTAINED FROM FDA IN 1999
HEMORRHAGIC DISORDERS
RECOMBINANT FACTOR VIIa

- ADVANTAGES OF r VIIa
  - NOT ENZYMATICALLY ACTIVE THUS DOES NOT ACTIVATE COAGULATION SYSTEMICALLY
  - ACTIVITY IS NOT AFFECTED BY NATURAL ANTI-COAGULANTS/INHIBITORS
  - SAFETY ADVANTAGE OVER PLASMA DERIVED FACTOR CONCENTRATES
HEMORRHAGIC DISORDERS
RECOMBINANT FACTOR VIIa

● OFF-LABEL USAGE:
  ● NEONATAL COAGULOPATHIES
  ● SEVERE HEPATIC DISEASE/ LIVER TRANSPLANTATION
  ● HIGH RISK SURGICAL PROCEDURES
  ● TRAUMATIC BLOOD LOSS
  ● BONE MARROW TRANSPLANTATION
  ● THROMBOCYTOPENIC BLEEDING
  ● PLATELET FUNCTION DISORDERS
  ● URGENT REVERSAL OF ANTICOAGULANTS
  ● CONGENITAL DEFICIENCIES OF V,VII,X,XI
  ● Von WILLEBRAND DISEASE W/INHIBITORS
HEMORRHAGIC DISORDERS
RECOMBINANT FACTOR VIIa

- NEONATAL / PEDIATRIC COAGULOPATHY
  - LIFE THREATENING HEMORRHAGE IN PRE-TERMS
    - SEVERAL CASE REPORTS / VARYING DOSES
    - BOLUS AND/OR REPETITIVE DOSES
    - 5-200 ug/Kg.....CESSATION OF BLEEDING, IMPROVED PT
    - WITHIN 10 MINS.....SUSTAINED TO 6 HRS
  - RETROSPECTIVE SERIES IN PEDIATRICS
    - 3 MONTHS - 19 YEARS
    - VARIABLE COAGULOPATHIES
    - 50-100 ug/Kg
    - CORRECTION OF LABORATORY PARAMETERS
HEMORRHAGIC DISORDERS
RECOMBINANT FACTOR VIIa

● HEPATIC DYSFUNCTION
  ● LAPAROSCOPIC LIVER BX-66 PATIENTS (MULTICENTER RCCT)
    ● EFFICACY OF 4 DOSES (5, 20, 80, 120 ug/Kg) ON CLINICAL AND LABORATORY PARAMETERS
    ● PT CORRECTED TO NORMAL IN MAJ. OF PTS
    ● HEMOSTASIS ACHIEVED IN 48/65 (74%) IN 10 MINS AND MAINTAINED FOR 1`8 HRS
    ● NO PTS NEEDE OPERATIVE INTERVENTION OR TRANSFUSIONS
  
● COAGULOPATHY OF FULMINANT HEPATIC FAILURE PRIOR TO LIVER T/PLANT (CASE CONTROLLED-HISTORICAL CONT)
  ● 15 PTS (8 PLASMA, 7 PLASMA + rVIIa)
    ● ALL PTS NORMALIZED THEIR PT IN THE rVIIa GROUP VS 0
HEMORRHAGIC DISORDERS
RECOMBINANT FACTOR VIIa

- HEPATIC DYSFUNCTION
  - NON-BLEEDING VOLUNTEERS W/CIRRHOSIS
    - DOSE ESCALATION STUDY/SINGLE CENTER
    - 10 PATIENTS W/ ELEVATED PT-3 SUCCESSIVE DOSES OF 5, 20, 80 ug/Kg-OVER 3 WEEKS
    - TRANSIENT NORMALIZATION OF PT IN ALL GROUPS...DOSE DEPENDENT DURATION

- BLEEDING ESOPHAGEAL VARICES
  - OPEN LABEL TRIAL (10 PTS -80 ug/Kg)
  - EFFECT ON PT
  - IMMEDIATE NORMALIZATION OF PT WITHIN 30 MINS IN ALL PATIENTS
HEMORRHAGIC DISORDERS
RECOMBINANT FACTOR VIIa

- ORTHOTOPIC LIVER TRANSPLANTATION
  - COMPLICATED BY COAGULOPATHY OF LIVER FAILURE + SURGERY
  - SINGLE CENTER OPEN LABEL STUDY
    - 6 PATIENTS X 80 ug/Kg IMMED.PRE-OP
    - REDUCED BLOOD COMPONENT USE VS HISTORIC CL
    - WELL TOLERATED
  - CASE REPORT OF SUCCESS IN WILSON’S DISEASE (2 PTS-50-6- ug/Kg IMMED PRE-OP)

- LIVER FAILURE + DIC
  - CASE REPORTS
    - CONCOMITANT BLEEDING ATTENUATED IN 2 CASE REPORTS ASSOCIATED WITH DIC
HEMORRHAGIC DISORDERS
RECOMBINANT FACTOR VIIa

- REVERSAL OF ANTICOAGULANT THERAPY
  - WARFARIN REVERSAL
    - 2 REPORTS (1 CASE REPORTS 1 AND SERIES OF 13 PTS)
      - IMMEDIATE REVERSAL OF INR IN 5 PTS
      - NO GREATER PERI-OPERATIVE BLEEDING- 5 PTS
      - IMPROVEMENT IN HEMORRHAGIC MANIFESTATIONS
  - FONDAPARINUX
    - ONE PCRT IN HEALTHY SUBJECTS (16 subjects)
      - 90 ug/Kg r VIIa (8) vs F+Placebo(4) vs rVIIa + Placebo(4)
      - NORMALIZATION OF PTT IN ALL rVIIa SUBJECTS
      - NORMALIZATION OF THROMBIN GENERATION
  - DIRECT ANTI-THROMBIN INHIBITORS
HEMORRHAGIC DISORDERS
RECOMBINANT FACTOR VIIa

- PERI-OPERATIVE /TRAUMATIC BLOOD LOSS (PROCEDURE ASSOCIATED OR COAGULOPATHIC)
  - USUALLY TRIED WHEN TRADITIONAL THERAPY FAILS
  - RETROPUBIC PROSTATECTOMY(DB-PCRCT)
    - REDUCTION IN PERIOPERATIVE BLOOD LOSS AND TX
      - DOSE DEPENDENT C/W PLACEBO (20 ug/Kg : 40 ug/Kg )
      - 40 ug/Kg NO TX VS 58% PLACEBO
  - CARDIAC VALVE SURGERY
    - 30 ug/Kg OPEN LABEL Q 3 hrs…..4 DOSES
      - REDUCED PT BY > 12 SECS
      - REDUCTIONS IN BLOOD LOSS AFETR SINGLE DOSE IN ALL
  - MISCELLANEOUS CASE REPORTS IN TRAUMA
    - MILITARY AND COMPLEX SURGERY
HEMORRHAGIC DISORDERS
RECOMBINANT FACTOR VIIa

- PLATELET DISORDERS
  - THROMBOCYTOPENIA
    - 74 PTS /PHASE I/II STUDY(IV BOLUS 50-100ug/Kg)
      - IMPROVEMENT IN BLEEDING TIMES IN PTS WITH PLATELET COUNTS < 20,000
      - CORRECTION OF BLEEDING EVENTS IN 6 PTS
    - 2 PTS W/SEVERE LIFE THREATENING HEMORRHAGE AND ITP
  - THROMBOCYTOPATHIA
    - 2 CASE REPORTS IN GLANZMANN’S THROMBASTHENIA
      - W/PROCEDURES incl SURGERY
HEMORRHAGIC DISORDERS
RECOMBINANT FACTOR VIIa

- OTHER COAGULOPATHIES
  - VON WILLEBRAND DISEASE
    - CONGENITAL
      - CASE REPORT WITH RECURRENT BLEEDING
    - ACQUIRED
      - INHIBITOR ASSOCIATED W/MGUS
  - HERMANSKY PUDLAK SYNDROME
  - FACTOR VII DEFICIENCY
  - FACTOR X DEFICIENCY W/AMYLOID
HEMORRHAGIC DISORDERS
RECOMBINANT FACTOR VIIa

- BONE MARROW TRANSPLANTATION
  - 2 REPORTS (BOLUS + INFUSIONAL)
    - PULMONARY HEMORRHAGE (1)
    - HEMORRHAGIC CYSTITIS (3)
    - GI BLEEDING (2)
    - DIFFUSE ALVEOLAR HEMORRHAGE (1)
<table>
<thead>
<tr>
<th>Study Setting</th>
<th>N</th>
<th>Treatment</th>
<th>Primary Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Thrombocytopenia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate to severe bleeding after allogeneic BMT</td>
<td>100</td>
<td>Std therapy + rFVIIa 40, 80, or 160 μg/kg or placebo</td>
<td>Change in bleeding score with time</td>
</tr>
<tr>
<td><strong>Trauma</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe blunt or penetrating trauma</td>
<td>280</td>
<td>Std therapy + 3 doses of rFVIIa</td>
<td>RBC transfusion in first 48 hours</td>
</tr>
<tr>
<td>ICH</td>
<td>80</td>
<td>rFVIIa 10, 20, 40, 80, or 120 μg/kg or placebo</td>
<td>Change in ICH volume 24 after hours</td>
</tr>
<tr>
<td><strong>Liver Disease</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cirrhosis with acute upper GI bleeding and portal hypertension</td>
<td>240</td>
<td>rFVIIa 100 μg/kg or placebo</td>
<td>Composite 5-day endpoint: control of GI bleeding, prevention of re-bleeding, mortality</td>
</tr>
<tr>
<td>Cirrhosis and partial heptectomy</td>
<td>240</td>
<td>rFVIIa 50 or 100 μg/kg or placebo</td>
<td>Perioperative RBC transfusion</td>
</tr>
<tr>
<td>Non-cirrhotic patients and partial heptectomy</td>
<td>180</td>
<td>Single dose of rFVIIa 20 or 80 μg/kg or placebo</td>
<td>Perioperative RBC transfusion</td>
</tr>
<tr>
<td>Patients undergoing liver transplantation</td>
<td>180</td>
<td>rFVIIa 60 or 120 μg/kg or placebo</td>
<td>Perioperative RBC transfusion</td>
</tr>
<tr>
<td><strong>Reversal of oral anticoagulant therapy</strong></td>
<td>210</td>
<td>rFVIIa 40 or 80 μg/kg or placebo</td>
<td>Bleeding 6 hours after treatment initiation</td>
</tr>
</tbody>
</table>
RECOMBINANT F VII a
SUMMARY OF APPLICATIONS

- ACTIVATED FVII/TF INTEGRAL IN NORMAL HEMOSTASIS
- AMPLIFIES BOTH PRIMARY AND SECONDARY COMPONENTS
- rVIIa REPLACEMENT THERAPY HAS SEVERAL BROAD POTENTIAL APPLICATIONS AND APPEARS TO BE SUCCESSFUL
- EVIDENCE OF EFFICACY OFF-LABEL IS MOSTLY ANECDOTAL
- SEVERAL TRIALS ARE UNDERWAY TO VALIDATE THE PERCEIVED THERAPEUTIC APPLICATIONS
NovoSeven: USAGE

- SINCE 1997 SALES HAVE INCREASED TENFOLD
  - WALL STREET JOURNAL 3/17/04

- APPLICATIONS
  - SEVERE BLEEDING FROM CAR ACCIDENTS
  - GUNSHOT WOUNDS
  - POST-SURGERY HEMORRHAGE

- IS IT THE NEW WONDER DRUG FOR HEMOSTASIS?
  - ANECDOTAL
  - NOVO NORDISK HAS PROVIDED LITTLE EVIDENCE ABOUT
    THE DRUGS SAFETY AND EFFICACY IN THESE
    UNAPPROVED USES