Management of the bleeding patient

Impact of anticoagulants
Impact of NOAC’s

• Approved in Orthopedic surgery prophylaxis
• Approved for chronic atrial fibrillation
• Approved for DVT therapy
• Acute coronary syndrome?
• Not approved for Cardiac Valves
• Penetrance of these drugs increasing >20%
Reversal of anticoagulant effect
WHY?

• Urgent Procedure (less than 6 hrs)
• Acute bleeding
• Acute trauma
• Urgent surgery with anticoagulants present
Important Principles

• Half life of drugs
• Metabolism – where? Renal clearance
• Warfarin – 36 hrs – antidotes available
• Rivaroxaban - (od) 12 hrs – reversal possible
• Apixaban - (bid) 12 hrs - reversal possible
• Dabigatran - (bid) 12 hrs - reversal difficult
Whether to try to reverse or wait it out is a **Clinical decision** as well as what options are available to you.
How do you know the anticoagulant effect is gone

- Warfarin - If INR <1.5 - probably OK
- Dagitran - If TT normal no drug. if TT not available a normal Ptt means very little drug
- Rivaroxaban - If INR normal little drug
- Apixaban - if INR normal little drug
- Anti Xa assays probably better but not readily available in many hospitals
Strong correlation between Prothrombin Time and plasma concentrations of rivaroxaban

Healthy human subjects

Adjusted from Kubitza et al., Eur J Clin Pharmacol 2005
How do I determine if my patient is anticoagulated?

- A 2.5-fold prolongation in aPTT correlates with an excessive anticoagulant effect\(^1,2\)
- No single test (aPTT, INR, TT, ECT) is adequate to reliably assess the anticoagulant activity of dabigatran following administration\(^1\)

\[
y = 0.86 + 0.06873^* \cdot x^{1/2} \\
r^2 = 0.8514
\]

\(aPTT = \) activated partial thromboplasmin time; ECT = ecarin clotting time; INR = international normalized ratio; TT = thrombin clotting time

Armamentarium for bleeding

- Blood products - RBC, Plasma, Platelets
- DDAVP
- Tranexamic Acid
- Prothrombin Complex
- Factor VIIa
- Activated PCC (aPCC)
- Antidotes ????
Drugs to review

- Warfarin
- Rivaroxaban
- Apixaban
- Dabigatran
Warfarin
Warfarin reversal

- Vitamin K
- Prothrombin complex
- NAC guidelines
- Ottawa data (STANDARD DOSING)
- 20cc = 500 units
Prothrombin complex

OCTAPLEX

Beriplex
**OCTAPLEX**

Human Prothrombin Complex, freeze dried
Powder and solvent for solution for injection

<table>
<thead>
<tr>
<th>One vial of OCTAPLEX for solution for injection contains:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Human Coagulation Factor II</td>
<td>220-760 IU</td>
</tr>
<tr>
<td>Human Coagulation Factor VII</td>
<td>180-480 IU</td>
</tr>
<tr>
<td>Human Coagulation Factor IX</td>
<td>400-620 IU</td>
</tr>
<tr>
<td>Human Coagulation Factor X</td>
<td>360-600 IU</td>
</tr>
<tr>
<td>Protein C</td>
<td>140-620 IU</td>
</tr>
<tr>
<td>Protein S</td>
<td>140-640 IU</td>
</tr>
</tbody>
</table>

Not Blood group specific
Figure 1. The median pre-treatment INR value for all 150 patients analyzed was 2.6 which corrected immediately to a median post-treatment value of 1.4. This correction was sustained for up to 27 hours.
## Results

Table 1. Characteristics of selected patients who received Octaplex.

<table>
<thead>
<tr>
<th>Patients</th>
<th>Non-CNS Bleeders</th>
<th>CNS Bleeders</th>
<th>Non-Bleeders</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
<td>54</td>
<td>32</td>
<td>64</td>
<td>150</td>
</tr>
<tr>
<td>Age (median, range)</td>
<td>78 (23-73)</td>
<td>79 (47-93)</td>
<td>76 (38-97)</td>
<td>78 (34-97)</td>
</tr>
<tr>
<td>Octaplex dose (median, (range)) (IU/kg)</td>
<td>13.8 (6.7-36.3)</td>
<td>13.7 (6.7-27.8)</td>
<td>13.3 (6.5-29.4)</td>
<td>13.8 (6.5-36.3)</td>
</tr>
<tr>
<td>Pre-INR (median (range))</td>
<td>2.6 (1.5-10)</td>
<td>3.0 (1.5-10)</td>
<td>2.4 (1.5-10)</td>
<td>2.6 (1.5-10)</td>
</tr>
<tr>
<td>Immediate post-INR (median (range))</td>
<td>1.5 (1.0-2.5)a,d</td>
<td>1.4 (1.2-2.2)p</td>
<td>1.4 (0.9-2.4)c</td>
<td>1.4 (0.9-2.5)</td>
</tr>
<tr>
<td>Post-treatment INR ≤ 1.5 (n (%))</td>
<td>31 (57)</td>
<td>24 (75)</td>
<td>47 (73)</td>
<td>102 (58)</td>
</tr>
<tr>
<td>Successful bleeding cessation (n (%))</td>
<td>40 (74)</td>
<td>16 (50)c</td>
<td>63 (98)</td>
<td></td>
</tr>
</tbody>
</table>
Recommendations

- If INR < 4.0
- Procedures - 40 cc adequate
- For surgery and bleeding patients
- 60-80cc
- NAC recommendations – keep changing
- Based on INR correction mainly
Reversal of Rivaroxaban and Dabigatran by Prothrombin Complex Concentrate
A Randomized, Placebo-Controlled, Crossover Study in Healthy Subjects

Elise S. Eerenberg, MD; Pieter W. Kamphuisen, MD; Meertien K. Sijpkens, BSc;
Joost C. Meijers, PhD; Harry R. Buller, MD; Marcel Levi, MD

Background—Rivaroxaban and dabigatran are new oral anticoagulants that specifically inhibit factor Xa and thrombin, respectively. Clinical studies on the prevention and treatment of venous and arterial thromboembolism show promising results. A major disadvantage of these anticoagulants is the absence of an antidote in case of serious bleeding or when an emergency intervention needs immediate correction of coagulation. This study evaluated the potential of prothrombin complex concentrate (PCC) to reverse the anticoagulant effect of these drugs.

Methods and Results—In a randomized, double-blind, placebo-controlled study, 12 healthy male volunteers received rivaroxaban 20 mg twice daily (n=6) or dabigatran 150 mg twice daily (n=6) for 2½ days, followed by either a single bolus of 50 IU/kg PCC (Cofact) or a similar volume of saline. After a washout period, this procedure was repeated with the other anticoagulant treatment. Rivaroxaban induced a significant prolongation of the prothrombin time (15.8±1.3 versus 12.3±0.7 seconds at baseline; P<0.001) that was immediately and completely reversed by PCC (12.8±1.0; P<0.001). The endogenous thrombin potential was inhibited by rivaroxaban (51±22%; baseline, 92±22%; P=0.002) and normalized with PCC (114±26%; P<0.001), whereas saline had no effect. Dabigatran increased the activated partial thromboplastin time, ecarin clotting time (ECT), and thrombin time. Administration of PCC did not restore these coagulation tests.

Conclusion—Prothrombin complex concentrate immediately and completely reverses the anticoagulant effect of rivaroxaban in healthy subjects but has no influence on the anticoagulant action of dabigatran at the PCC dose used in this study.

Clinical Trial Registration—URL: http://www.trialregister.nl. Unique identifier: NTR2272. (Circulation. 2011;124:00-00.)
Effect of PCC

Rivaroxaban 20mg BID for two and a half days

PCC or placebo infusion
Rivaroxaban

• Not a lot of data
• T1/2 - 9 hrs
• Excreted by kidneys and gut
• Protamine not very effective
• Factor VIIa in Urgent situations and major bleeding (some data)
• PCC - 100-120cc = 2000-2500 u factor X
• Little clinical data but makes physiologic sense
Apixaban

- Approved for atrial fibrillation
- Bioavailability 66%
- Protein binding 88%
- T½ 8-15 hours
- Renal excretion 25%
- Dosing BID
- Reversal – PCC same dose
The future – anti-Xa antidote

- Portola
- Modified X molecule
- No anticoagulant effect
- No thrombotic effect
- Binds all anti Xa drugs
- Phase 3 tests underway
Reversal of Dabigatran effect

Is there a clear answer?
Effect of PCC
Thromboelastogram - melagatron
Dabigatran Reversal

- Drugs have little measurable reversal effect
- Needs different approach
- Effect needed at bleeding site
- Needs substrate and thrombin
- Block normal thrombolysis
PCC and Factor VIIa
Dabigatran

• Not a lot of clinical data – only opinion and case reports
• Most effect appears to be Factor VIIa or aPCC
• Dialysis ??
• Our current approach
• PCC with VIIa (60cc and 4 or 5mg VIIa)
• Tranexamic acid
• Clinical effect monitored - not tests
• Antidote – specific antibody – phase 1 complete
What to do when bleeding

• Clinical! Clinical! Clinical!!!

• If bleeding not in a vital spot and not exanguinating support with blood products and wait out half life

• Tests tell degree of anticoagulation

• Tests tell you likely T1/2 you are dealing

• IF cannot stem bleeding

• Use best available therapy.
Conclusions

• Even more drugs coming
• Few “antidotes” but coming
• Tests reflect presence of drug
• Indirectly – level of drug
• Do not predict bleeding
• Help in choosing best therapy
• Armamentarium for hemostatic products (availability ?)
• Remember - patients were likely receiving these drugs for a valid reason which likely has not changed and will need to be restarted
Massive transfusion protocol
Massive transfusion protocols

• Many hospitals have
• Outline guidelines for product dispensing and timing.
• Need updating as experience develops.
• Need updating as new products emerg.
• Europe is different from North America
Management of Patients with Critical Bleeding with Coagulopathy and Massive Transfusion Requirement

Identify and manage surgical bleeding i.e. Surgery, Angiographic Embolization, Endoscopy

### Appropriate Conventional Medical Interventions
- Admit patient to acute monitor bed
- Venous accesses with volume replacement
- Prevent and reverse hypothermia
- Prevent and reverse acidosis
- Correct coagulopathy
- Heparin reversal
  - Protamine 1 mg IV /100 units of heparin
- Warfarin reversal
  - Octaplex & Vitamin K 5 mg IV
- Consider antifibrinolytic agents
  - Tranexamic acid 10 mg/kg IV
- CRF and Von Willebrand’s Disease
- DDAVP 0.3 mcg/kg IV x 1

### Laboratory Tests
<table>
<thead>
<tr>
<th>Baseline CBC, INR, PTT, TT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Repeat blood test after each 4-6 units RBCs</td>
</tr>
<tr>
<td>INR &gt; 1.5</td>
</tr>
<tr>
<td>Give 6 units FP</td>
</tr>
<tr>
<td>Fibrinogen &lt; 1 g/L</td>
</tr>
<tr>
<td>Give 10 -15 units of Cryoprecipitate</td>
</tr>
<tr>
<td>Platelet count &lt; 50 X 10^9/L</td>
</tr>
<tr>
<td>Give 1 dose of Platelets</td>
</tr>
<tr>
<td>Consider Calcium Chloride</td>
</tr>
<tr>
<td>1 gm IV slowly</td>
</tr>
</tbody>
</table>

### If bleeding and coagulopathy continue after conventional therapy
- Usually:
  - 10 units RBC
  - 6 units FP
  - 1-2 doses Platelets
  - 10 units Cryoprecipitate

### Phone # 14328
Transfusion Medicine
- Consider rFVIIa 4 mg
  - If no response in 20min
    - Surgery optimized?
    - Consider 2nd dose rFVIIa 4 mg
Massive transfusion guidelines

• Makes clinicians aware
• What does literature say.
• May save some products?
• Does not influence survival
What does work

• Early intervention (CODE BLEED)
• Limit crystalloid
• Damage control – not definitive intervention
• Early plasma or PRBC
• Keep patient warm
• Support or transfer – Clinical decision
Bleeding in Rural hospital

- Armamentarium
- RBC
- PCC
- Tranexamic acid
- Number to call – assistance always available
QUESTIONS ???