

Anticoagulation: A Review of Pathways and Reversal Agents

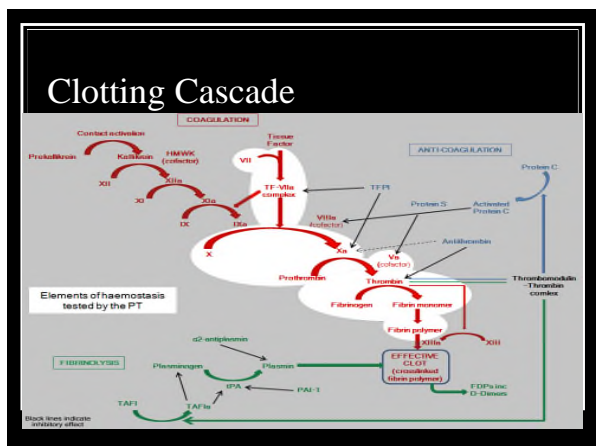
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Objectives

- Appreciate the importance of hemostasis
- Gain a basic understanding of the clotting cascade
- Gain familiarity with heparin, low molecular weight heparin, target specific oral anticoagulants, and warfarin
- Understand the mechanism of action and place in therapy of pharmacologic reversal agents
- Realize that reversal of anticoagulation does NOT alleviate the underlying process of hemorrhage.

What is Hemostasis

- Definition:
 1. The stoppage of bleeding or hemorrhage.
 2. The stoppage of blood flow through a blood vessel or body part.



- ### Laboratory Assessment
- Hemoglobin/Hematocrit
 - aPTT
 - PT
 - INR
 - Thromboelastography (TEG®)

- ### PT, aPTT, and INR
- aPTT primarily used for dysfunction of intrinsic pathway
 - PT & INR primarily used to define deficiencies of the extrinsic pathway
 - Very effective for respective determinations
 - Each is limited and neither give a complete assessment of coagulopathy

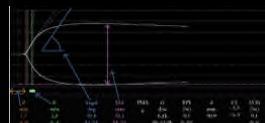
Thromboelastography (TEG[®])

- NOT a new test
- Evaluates coagulation of whole blood.
- Multiple variables reported
- Graphical representation available
- Provides guidance for transfusion

(TEG[®]) Parameters

- R Value - Time to clot initiation
- K Value - Time to 20 mm
- α Angle – Angle between R and K values
- MA – Clot Strength
- LY30 – Fibrinolysis in 30 minutes
- Platelet Mapping
 - AA inhibition
 - ADP Inhibition

Graphic Representation



How does this help????



Re-establishing Hemostasis

- Tamponade/pressure
- Blood products
- Surgical intervention
- Pharmacologic manipulation

Blood Products

- Packed Red Blood Cells (PRBC's)
- Fresh Frozen Plasma (FFP)
- Platelets
- Cryoprecipitate



Packed Red Blood Cells

- Are required for oxygen delivery
- Are necessary for hemodynamic stability
- Useful as a volume expander
- Do **NOT** re-establish hemostasis

Fresh Frozen Plasma

- Contains clotting factors
 - II
 - VII
 - VIII
 - IX
 - XIII
- Contains fibrinogen (Factor I)
- Contains von Willebrand Factor (vWF)

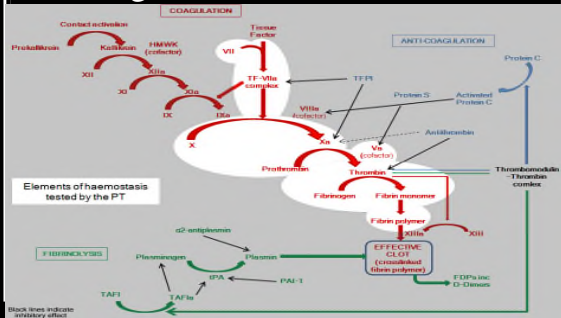
Platelet Transfusions

- Derived from whole blood
 - Single donor
 - Multiple donor
- Do **NOT** contain clotting factors
- Necessary to maintain a stable clot
- Usually reserved for active hemorrhage or platelet counts < 50k

Cryoprecipitate

- Small volume
- Manufactured by thawing FFP
- Higher concentration of clotting factors
- Used primarily to replete fibrinogen

Clotting Cascade



Confounding Medications

- | | |
|-------------------------|---------------------------|
| ■ Heparin (Liquaemin®) | ■ Rivaroxaban (Xarelto®) |
| ■ Enoxaparin (Lovenox®) | ■ Apixaban (Eliquis®) |
| ■ Dalteparin (Fragmin®) | ■ Edoxaban (Savaysa®) |
| ■ Warfarin (Coumadin®) | ■ Fondaparinux (Arixtra®) |
| | ■ Dabigatran (Pradaxa®) |

Heparin (Liquaemin®)

- Increases activity of ATIII
- Monitored by aPTT
- Onset: Immediate
- $T_{1/2}$: 45 minutes
- Indications:
 - Atrial fibrillation
 - Treatment/prevention of DVT/PE



Enoxaparin (Lovenox®)

- Activates ATIII and inhibits Xa
- Monitor through Anti-Xa levels
- Onset: 3-5 hours
- $T_{1/2}$: ~12 hours
- Indications
 - Atrial fibrillation
 - Treatment/prevention of DVT/PE



Dalteparin (Fragmin®)

- Activates ATIII and inhibits Xa
- Monitor through Anti-Xa levels
- Onset: 3 minutes
- $T_{1/2}$: 10-24 hours
- Indications
 - Atrial fibrillation
 - Treatment/prevention of DVT/PE

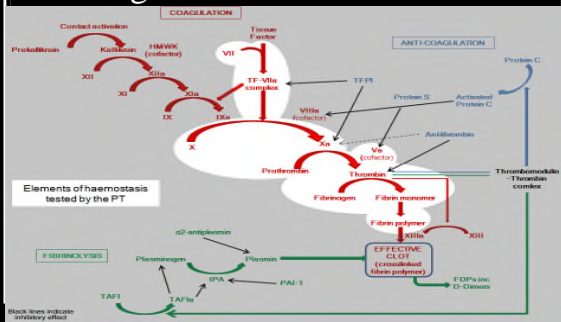


Protamine sulfate

- Used for heparin over anticoagulation
- Neutralizes heparin by forming stable complexes
- 1 mg of Protamine neutralizes ~ 100 units of heparin
- Administration is *slow IV push*
- Maximum of 50 mg dose



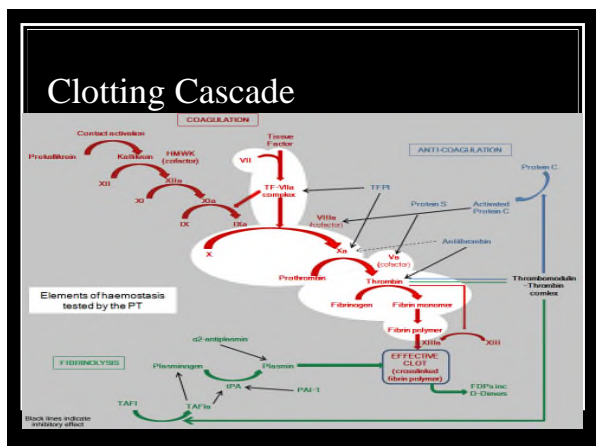
Clotting Cascade



Warfarin (Coumadin®)

- Blocks activation of vitamin k dependent clotting factors
- Decreases speed of clotting
- Does NOT cause bleeding
- Indications
 - Atrial fibrillation
 - PE/DVT
 - Mechanical valve replacement
 - Intrinsic clotting disorders





Warfarin Reversal

- INR between 4.5 and 10 and with no evidence of bleeding, we suggest against the routine use of vitamin K
- INRs > 10.0 and with no evidence of bleeding, we suggest that oral vitamin K be administered
- For major bleeding, we suggest rapid reversal of anticoagulation with four-factor PCC rather than with plasma
- Use of vitamin K 5 to 10 mg administered by slow IV injection rather than reversal with coagulation factors alone

Chest. 2012;141(7 suppl):e183C-e184S.
doi:10.1378/chest.11.2295


Vitamin K (Mephyton®)

- Naturally produced by enteric flora
- Provides vitamin K for synthesis of specific clotting factors
- 1-25 mg IV or PO (max 50mg)
- For reversal of warfarin induced bleeding
- Also indicated for other types of hypoprothrombinemia

(Gallap et al, 1980)


Recombinant Factor VIIa (NovoSeven®)

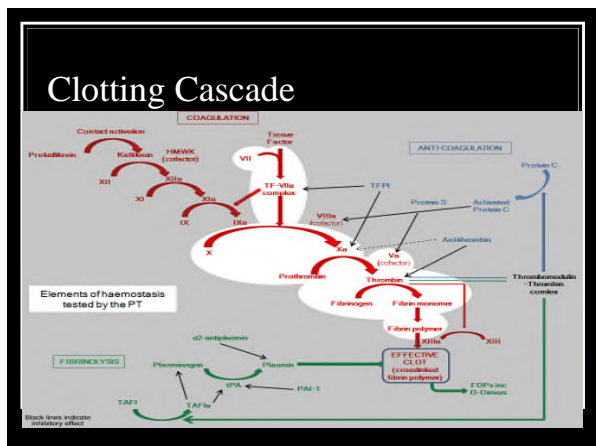
- Multifactorial mechanism
- Doses range from 1 mg to 120 mcg/kg
- Indications
 - Hemophilia A & B
 - Factor VII deficiency
- Therapeutic uses
 - Cardiothoracic surgery
 - Neurosurgery
 - Hemorrhage secondary to trauma



4 Factor PCC (Kcentra®)

- Approved for warfarin reversal
- Contains II, VII, IX, and X
- Also contains Proteins C & S
- Single dose based on INR and patient's actual weight
- Maximum dose 5000 Units IV X 1.





Target Specific Oral Anticoagulants TSOAC's

Xa Inhibitors

- Rivaroxaban (Xarelto®)
- Apixaban (Eliquis®)
- Edoxaban (Savaysa®)
- Fondaparinux (Arixtra®)

Direct Thrombin Inhibitors

- Dabigatran (Pradaxa®)
- Argatroban

Rivaroxaban (Xarelto®)

- Inhibitor of Xa
- No monitoring available
- No direct reversal agent
- T_{1/2} ~8 hours
- Indications
 - Non-valvular Atrial fibrillation
 - Treatment of DVT/PE




Apixaban (Eliquis®)

- Inhibitor of Xa
- No monitoring available
- No direct reversal agent
- T_{1/2} ~12 hours
- Indications
 - Non-valvular Atrial fibrillation
 - Treatment of DVT/PE




Edoxaban (Savaysa®)

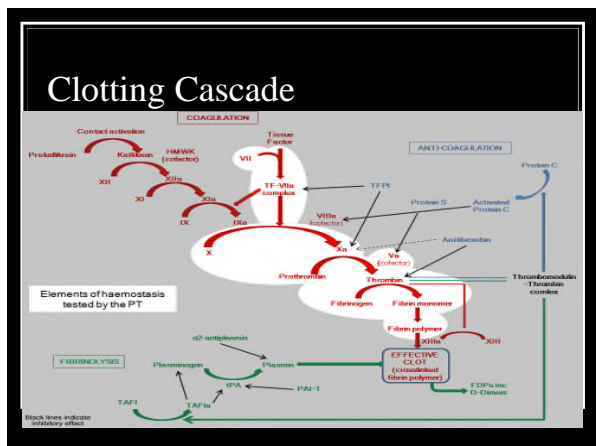
- Inhibitor of Xa
- No monitoring available
- No direct reversal agent
- T_{1/2} ~10 hours
- Indications
 - Non-valvular Atrial fibrillation
 - Treatment of DVT/PE



Fondaparinux (Arixtra®)

- Selectively inhibits Xa
- No monitoring available
- No direct reversal agent
- Onset: 2-3 hours
- T_{1/2}: ~18 hours
- Indications
 - Atrial fibrillation
 - Treatment of DVT/PE





Just reverse them

- FFP should work.....
- How about cryoprecipitate?
- Maybe some vitamin K
- I know...injectable Xa...
- Is there injectable thrombin?

Literature for Reversal

- Eerenberg ES, Kamphuisen PW, Sijpkens MK, Meijers JC, Buller HR, Levi M. Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate.
 - 12 healthy volunteers
 - Administered PCC
 - Reversal of prothrombin time
- Guideline for Reversal of Antithrombotics in Intracranial Hemorrhage
 - We suggest administering 4-factor PCC or activated PCC over rFVIIa because of the lower risk of adverse thrombotic events.
 - We suggest administering a 4-factor PCC (50 U/kg) or activated PCC (50 U/kg) if intracranial hemorrhage occurred within 3–5 terminal half-lives of drug exposure or in the context of liver failure.

Neurocrit Care (2015) 24:8–26
 Circulation. 2011;124:1573-1579

Factor Eight Inhibitor Bypassing Activity (FEIBA®)

- Factor Eight Inhibitor Bypassing Activity (FEIBA®)
 - FDA Labeled
 - Hemophilia A and B patients with inhibitors for:
 - Control and prevention of bleeding episodes
 - Perioperative management
 - Routine prophylaxis to prevent or reduce the frequency of bleeding episodes.
 - Non-FDA
 - Reversal of target specific oral anticoagulants

Factor Eight Inhibitor Bypassing Activity (FEIBA®)

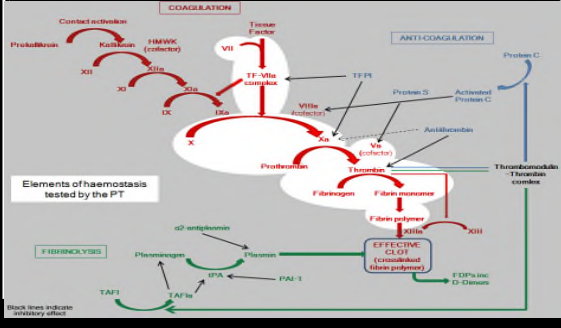
- Contains inactive factors II, IX, X
- Contains small amounts of activated factor VII
- Does NOT contain heparin nor Proteins C&S.
- Maximum dose 200 units/kg/day

Recombinant Factor VIIa (NovoSeven®)

- Multifactorial mechanism
- Doses range from 1 mg to 120 mcg/kg
- Indications
 - Hemophilia A & B
 - Factor VII deficiency
- Therapeutic uses
 - Cardiothoracic surgery
 - Neurosurgery
 - Hemorrhage secondary to trauma



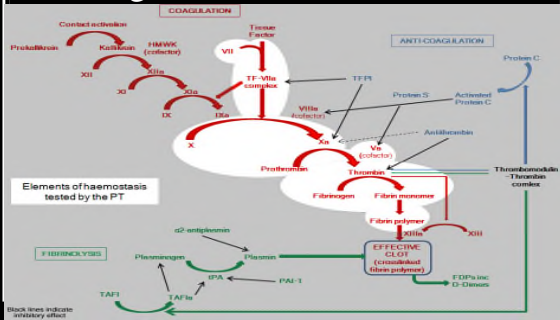
Clotting Cascade



Dabigatran (Pradaxa®)

- Inhibits thrombin activity
- No monitoring available
- No direct reversal agent
- T1/2 ~12 hours
- Indications
 - Non-valvular Atrial fibrillation
 - Treatment of DVT/PE

Clotting Cascade



Idarucizumab (Praxbind®)

- Monoclonal antibody
- Designed SPECIFICALLY for (Pradaxa®)
- Binds directly to Pradaxa® and inactivates it
- Dosing is 2.5 grams IV x 2 doses
- *Theoretically* complete reversal



Tranexamic acid (CYCLOKAPRON®)

- Antifibrinolytic
- 10 mg/kg 3-4 times/day
- Hemophilia
- Multiple therapeutic uses
- Duration nearly 24 hours

Anderson et al, 1965)(Okamoto et al, 1964); (Anderson et al, 1968)(Verstraete, 1985).

Aminocaproic acid (Amicar®)

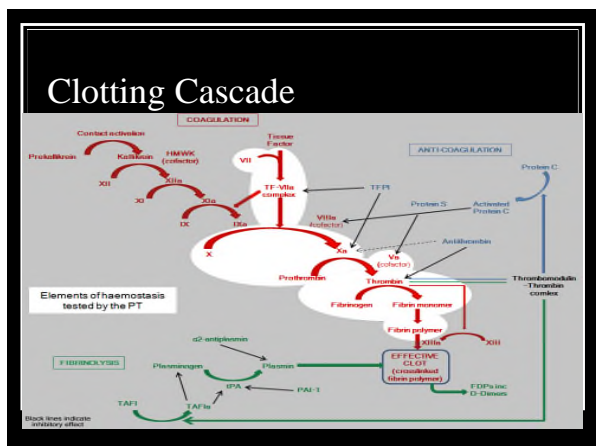
- MOA: displaces plasminogen from the fibrin surface resulting in antifibrinolytic effects.
- Onset: ~ 5 minutes
- Duration: 2 hours
- Inhibits profibrinolysin activity
- 4-5 grams followed by 1 gram/hr infusion for 8 hours
- Indicated for hemorrhage
- Limited scope of activity
- Duration

(Fodstad et al, 1981)(Post et al, 1977).

Conjugated estrogens

- Mechanism not completely understood
- 10 mg/day slow infusion
- Indications
 - Bleeding in renal failure
 - Postoperative hemorrhage
 - Hemorrhagic cystitis
 - Intractable vaginal bleeding
- Place in therapy

(Heunisch et al, 1998; Boyd et al, 1996; Shemin et al, 1990; Livio et al, 1986; Liu et al, 1984)



Optimizing therapy

- pH
 - >7.2
- Temperature
 - Euthermic
- Calcium
 - Serum=8.4-10.2 mg/dL
 - Ionized=1.1-1.3 mmol/L
- Fibrinogen
 - >100 mg/dL
- Platelets
 - >100,000/uL

Meng et al 2003, Boffard et al 2005

Conclusion

- Multiple modalities are often required to re-establish hemostasis.
- **EARLY** intervention and resuscitation are paramount.
- Reversal of anticoagulants **ONLY** returns patients to baseline hemorrhagic risk.

Questions?



References

- Evidence-based management of anticoagulant therapy Holbrook A, Schulman S, Witt DM, et al. *Chest*. 2012;141(2_suppl):e152S-e184S. doi:10.1378/chest.11-2295.
- Eerenberg ES, Kamphuisen PW, Sijkens MK, Meijers JC, Buller HR, Levi M. Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate. *Circulation*. 2011;124:1573Y1579.
- Guideline for Reversal of Antithrombotics in Intracranial Hemorrhage : A Statement for Healthcare Professionals from the Neurocritical Care Society and Society of Critical Care Medicine. Frontera JA, Lewin JI, Rabenstein AA, Aisiku IP, Alexandrov AW, Cook AM, Del Zoppo GJ, Kumar MA, Peerschke EI, Stiefel MF, Teitelbaum JS, Wartenberg KE, Zerfoss CL. *Neurocrit Care*. 2016 Feb;24(1):6-46. doi: 10.1007/s12028-015-0222-x
