Reversal of Oral Anticoagulants

A review of current strategy

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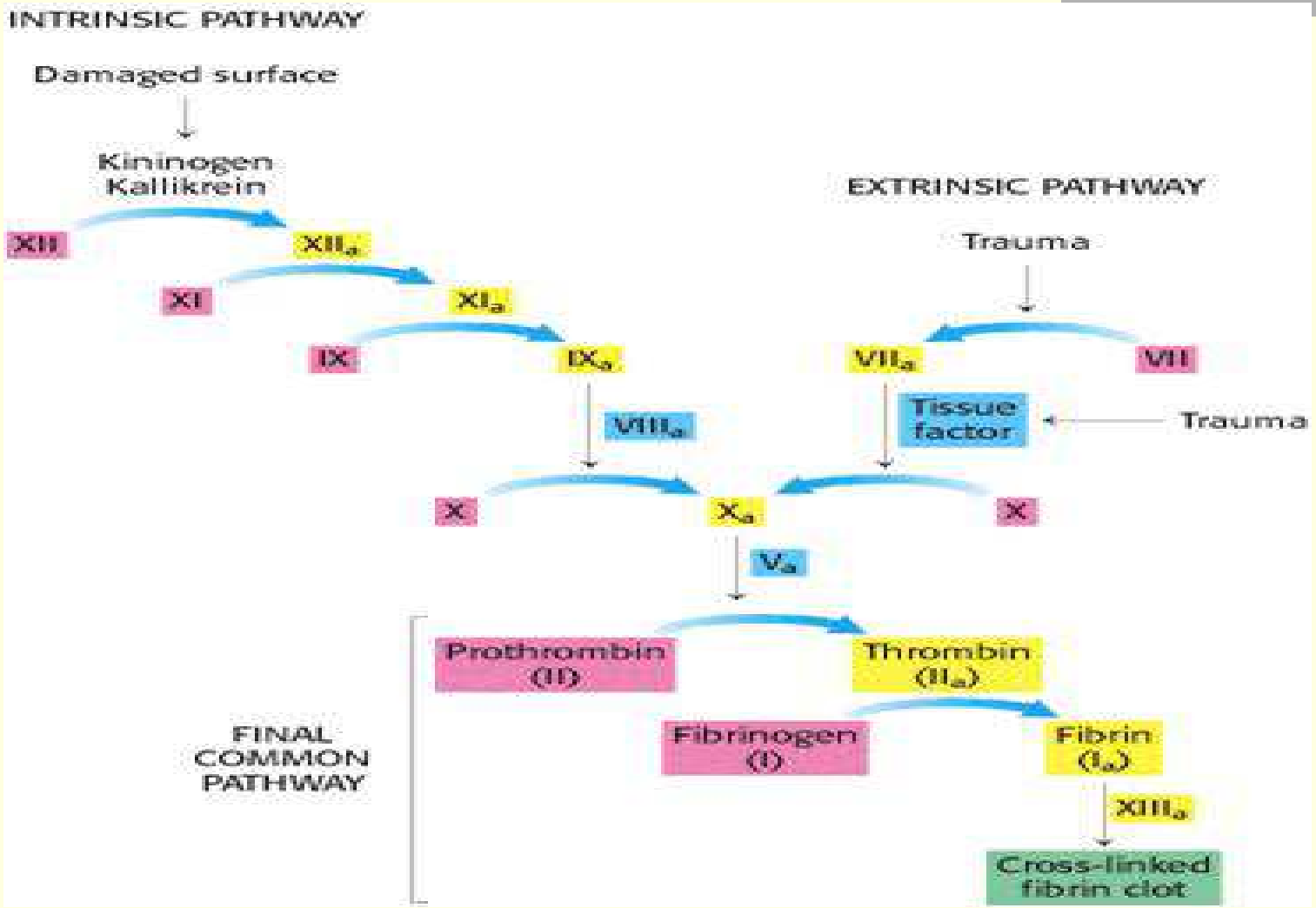
Objectives

- Overview of hemostasis
- Discussion of how oral anticoagulant agents fit into the clotting cascade
- Reversal strategies
- Emerging therapies

Overview of Hemostasis

- Virchow's Triad
  - Venous Stasis
  - Hypercoaguability
  - Endothelial Injury
- Hemostasis
  - Vasoconstriction
  - Platelet formation
  - Blood clot formation

Overview of Hemostasis



Oral Anticoagulant Agents

- Novel Oral Anticoagulants
  - Direct thrombin (factor IIa) inhibitor
    - Pradaxa (dabigatran)
  - Factor Xa inhibitors
    - Xarelto (rivaroxaban)
    - Eliquis (apixaban)
- Traditional Oral Anticoagulants
  - Vitamin K antagonist
    - Coumadin/Jantoven (warfarin)

Direct Thrombin Inhibitor

- Pradaxa (dabigatran etexilate)
  - Prodrug that is converted by the liver to the active dabigatran, a specific, reversible, direct thrombin inhibitor that inhibits both free and fibrin-bound thrombin.
  - Half-life of 12-14 hours
  - Substrate of P-glycoprotein efflux transporter system
    - Dose adjustment, avoidance, or relative contraindication with concomittant use with inhibitors
      - Amiodarone, atorvastatin, azithromycin …

Direct Factor Xa Inhibitors

- Xarelto (rivaroxaban)
  - Inhibits platelet activation and fibrin clot formation via direct, selective and reversible inhibition of factor Xa in both the intrinsic and extrinsic coagulation pathways
  - Half life of 5-9 hours
  - Substrate of CYP 3A4 (major) and P-glycoprotein
- Eliquis (apixiban)
  - Half life of 2.5 mg single dose ~8 hours
  - Half life of 5 mg single dose ~15 hours
  - Substrate of CYP 3A4 (major), P-glycoprotein, and to a lesser extent CYP1A2, 2C8, 2C9, 2C19, and 2J2 to inactive metabolites; and breast cancer resistant protein (BCRP)

Vitamin-K Antagonist

- Coumadin/Jantoven (warfarin)
  - Reduces synthesis of active clotting factors II, VII, IX, and X as well as proteins C and S in the liver by competitively inhibiting the vitamin K epoxide reductase complex
  - Half life 20-60 hours
  - Primarily 2C9 metabolism
    - Genomic variants have 37-70% reduction in clearance of warfarin
    - VKORC1 polymorphism *A haplotype* results in decreased doses of warfarin

Reversal Strategy Agents

- Prothrombin Complex Concentrate
  - 4-Factor PCC
    - Activated
      - ***FEIBA*** (factor VIII inhibitor bypassing activity)
      - Provides both factor II (prothrombin) and factor Xa for thrombin generation
      - Peak thrombin generation at 15-30 minutes
      - Duration of 8-12 hours
      - Off-label use for reversal of Pradaxa
    - Unactivated
      - ***Kcentra***
      - Provides factors II, VII, IX, and X along with proteins C and S
      - Onset of action is rapid with significant INR decline within 10 minutes
      - Duration of 6-8 hours
      - Labeled for reversal of anticoagulation with VKAs
  - 3-Factor PCC
    - Unactivated
      - ***Profilnine, Bebulin***
      - Provides factors II, IX, and X
      - Onset of action 10-30 minutes
      - Duration 12-24 hours
      - Off-label use for reversal of VKA when used with FFP or rFVII

Reversal Strategy Agents

- Factor Replacement
  - Recombinant Factor VIIa (rFVIIa, NovoSeven)
    - Onset of action 2 hours
    - Duration 10 – 12 hours
- Blood Product
  - Fresh Frozen Plasma
    - Contains factors II, VII, IX, and X
    - Onset is immediate
    - Duration 4-6 hours
- Vitamin K (phytonadione)
  - Pharmacokinetics relative to administration route
    - Onset 1-2 hours (IV) 6-10 hours (PO)
    - Peak INR reversal at 12-24 hours
      - Duration of vitamin K reversal effects is dose-related
    - Subcutaneous administration found to be equivalent to placebo in reversing INR

Reversal Strategy Review

- Direct Thrombin Inhibitors
  - Time
  - Activated Charcoal
    - Administer within two hours of ingestion
  - Dialysis
    - ~ 60% removed after 2-3 hours; diuresis and charcoal hemofiltration suggested
  - Prothrombin Complex Concentrate
    - FEIBA reversed anticoagulation in healthy subjects; one case study
    - Kcentra did not reverse anticoagulation in healthy subjects
  - Factor VIIa
    - Limited data suggest high doses may be effective in slowing bleeding; however not conclusive as a sole treatment
  - Antidote
    - In development. Consists of dabigatran Fab fragments analogous to digoxin antidote

Reversal Strategy Review

- Direct Factor Xa Inhibitors
  - Time
  - Activated Charcoal
    - Administer within two hours of ingestion
  - Prothrombin Complex Concentrate
    - FEIBA reversed anticoagulation in healthy subjects
    - Kcentra reversed anticoagulation in healthy non-bleeding subjects
  - Antidote
    - Recombinant, truncated form of Xa that binds with anti-Xa molecule at subnanomolar affinity

Reversal Strategy Review

- Warfarin
  - Vitamin K
    - Route of administration relative to INR
      - 5 – 9 without bleed = 1 – 2.5 mg PO recommended
      - > 9 without bleed = 2.5 – 5 mg PO recommended
      - Significant bleed = 10 mg IV recommended
    - Duration of vitamin K reversal effects is dose-related
  - Kcentra (4-factor PCC)
    - Dose is relative to INR elevation and should be given concurrently with vitamin K
      - 2 - <4 = 25 units/kg (max 2500 units)
      - 4 – 6 = 35 units/kg (max 3500 units)
      - > 6 = 50 units/kg (max 5000 units)
  - FFP, Factor VIIa, 3-factor PCC
    - May be useful in situations where Kcentra is not available.

Conclusions

- Lack of any substantial evidence to support use of PCC, FFP, FEIBA, rFVIIa in reversing the novel oral anticoagulant agents
- In emergency settings where the management of bleeding related to the new oral anticoagulant agents is required, protocol-driven pharmacological management should be established to aid clinicians in appropriate use of PCCs, FFP, FEIBA, rFVIIa and Vitamin K
- Controlled trials in patients with active bleed are warranted before any strong recommendations can be made regarding the appropriate use of reversal agents

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