Anticoagulation Reversal

Family Medicine Update  Big Sky, Montana
January, 2014
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Outline
Common anticoagulants
- coumadin
- ASA
- ADP Inhibitors
- DTI/XaI
Procoagulants
- novoseven
- TXA

misc anticoagulants
- IIb/IIIa inhibitors
- LMWH
- heparin
- associated with disease states
- liver disease
- uremia
- DIC

Premise
Premise of this lecture is that you have a patient with a life-threatening bleeding complication associated with a coagulopathy
How aggressive you are in any individual patient always relies on clinical judgment

Coumadin
Risk of major bleeding is 1-3 % per year
Varies depending on the intensity of the anticoagulation and patient risk factors

Vitamin K
Give IV
previous incidence of anaphylaxis was secondary to a diluent which is no longer present in the drug
PO better than SC
Onset 12-24 hours
Duration 12-24 hours

Coumadin
Vitamin K 10 mg IV
FFP 2 units IV
PCC 25 units/kg IV
**FFP**

- Dosing guidelines not accurate
- Recommend 2 units to start and redose
- Onset 30-60 minutes
- Duration 2-4 hours

**PCC**

- Prothrombin-complex concentrate
- Factor IX complex (Profilnine 9)
- INR < 4: 25 units/kg
- INR > 4: 50 units/kg
- Onset 10 minutes
- Duration 60 minutes

**Coumadin Reversal Protocol**

- Order the Vit K, FFP, PCC
- Repeat INR 10 minutes after PCC finished
- Give an additional 25 u/kg of PCC if INR still too high
- To OR with FFP hanging
- Follow INR Q 4 hours and give additional FFP if INR rebounds

**PCC**

- It is a medicine not a blood product
- Dispensed by pharmacy not blood bank
- Long shelf life
- Expensive
- PCC-3 (3 factor PCC)
- PCC-4 (4 factor PCC)
- PCC-3 plus aVIIr
- Should be a better hemostatic product but no evidence based recommendations for use
- Very Expensive

**Aspirin**

- Many of our patients are on ASA and many of those on another anticoagulant as well
- The increased risk of bleeding with the addition of ASA is unclear
Risk of ICH

ASA plus Coumadin
One study of 10,000 elderly risk increased threefold
0.3 % to 0.9 % per year
Another large case-control study showed no increased risk

ASA

Affects the platelet in the bone marrow at the time the platelet was formed
not a circulating effect
Not dose dependent
7 day lag
The patient on 81 mg ASA q day for at least 7 days = full antiplatelet effect
Acute ASA overdose = no antiplatelet effect

Aspirin

7 day irreversible platelet dysfunction
Platelet dysfunction test (replaces bleeding time)
add reagents (ADP, epi) and measure time to aggregation

ASA reversal

One unit single donor platelets

ADP Inhibitors

clopidogrel (Plavix)
prasugrel (Effient)
ticagrelor (Brilinta)
ticlopidine (Ticlid)

ADP Inhibitors Bleeding Risk

Incidence of major bleeding reported as 4-5 %
Limited data on drug effects once a bleeding event has occurred
Limited data on how to reverse antiplatelet effect
P2Y12 Platelet Function Test
reported as % inhibition
Considered reversed if < 20 %
Test not accurate if:
- Hgb < 26 %
- platelet count < 50,000
- if received Glycoprotein IIb/IIa inhibitor
  - Integrillin within 48 hours
  - Reopro with in 10 days

ADP Inhibitor reversal
desmopressin (DDAVP) IV 24 mcg
1 unit of single donor platelets

Direct Thrombin Inhibitors / Factor Xa Inhibitors
DTI/Xa
- dabagatran (Pradaxa)
- rivaroxaban (Xarelto)
- apixaban (Eliquis)

Direct Thrombin Inhibitors / Factor Xa Inhibitors
DTI/Xa Reversal
Limited data
- PCC 50 units/kg
- Recommend PCC4 if available else give PCC3
- Can add 1 mg of rVIIa to PCC3 to make PCC4

Dabigatran
- PCC 50 units/kg
- 4 hours of hemodialysis may remove up to 68 % of active drug
- Half-life depends on creatinine clearance
  - CrCl > 50: 24 hours
  - CrCl < 50: 48-96 hours
- MAO: DTI

Rivaroxaban
- PCC 50 units/kg
- Half life 5-9 hours if hepatic and renal function (CrCl > 80) are normal
- Half life 11-19 hours if elderly
- Half life 48+ hours if hepatic/renal failure
- MOA: Xa
apixiban
PCC 50 units/kg
Half life 12 hours if normal hepatic and renal function
Half life 48+ hours if elderly or hepatic/renal failure
MOA: XaI

Procoagulants
Novoseven
TPX
PCC (discussed earlier)

Novoseven
Recombivent activated factor VII rVIIa
A lot of enthusiasm when first released
No evidence based guidelines about how to use
Small case studies used in a variety of settings

Novoseven in trauma
Small series showed benefit
Best results in diffuse multifocal oozing
Not helpful in large vessel bleeding
No longer used much

Novoseven in ICH
Decreased the size of the intracranial hemorrhage by imaging criteria
No benefit in clinical recovery
Studied in both coumadin and non-coumadin bleeds without clear benefit

Novoseven use
To be effective must reverse:
acidosis
hypofibrinogenemia
hypothermia
Should only be used after 10 u RBC and adequate FFP, platelets and cyro
**Dose rFVIIa**

30-90 mcg/kg  
Dose can be repeated in 30 minutes  
New evidence indicates smaller doses just as effective as larger doses  
3,000 - 9,000 dollars a dose

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**Tranexamic acid (TXA)**

Inhibits fibrinolysis by competitively inhibiting plasmin activity and plasminogen activation  
Half-life approximately 2 hours  
Multiple dosing regimens are employed based on indication  
Tranexamic acid is associated with cerebral infarction in studies of patients with subarachnoid hemorrhage; however, thromboembolism with the use of tranexamic acid is rare

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**CRASH 2**

Multicenter RCT 20,211 adult trauma patients with, or at risk of, significant bleeding within 8 h of injury to either tranexamic acid or placebo  
Loading dose 1 g over 10 min then infusion of 1 g over 8 h

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**CRASH 2 Entrance Criteria**

Adult trauma patients with significant hemorrhage systolic blood pressure <90 mm Hg or heart rate >110 beats per min, or both, or who were considered to be at risk of significant hemorrhage, and who were within 8 h of injury

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**CRASH 2 Results**

All-cause mortality was significantly reduced with tranexamic acid  
14.5% vs 16.0%; relative risk 0.91, 95% CI 0.85–0.97; p=0.0035  
The risk of death due to bleeding was significantly reduced  
4.9% vs 5.7%; relative risk 0.85, 95% CI 0.76–0.96; p=0.0077

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**Ilb/IIa inhibitors**  
LMWH  
Heparin
**Glycoprotein IIb/IIIa**

Antibodies and receptor antagonists
Strategies for reversal dependent on individual agents half-lifes and unbound fractions

- abciximab
- eptifibatide
- tirofiban
- orbofiban*
- sirofiban*

*not available in US yet

**abciximab (Reopro)**

Biological half-life 8 hours
Unbound fraction low
- Platelet transfusion will reverse

**eptifibatide (Integrillin)**

tirofiban (Aggrastat)

Biological half-life is 4 hours
Unbound fraction large meaning platelet transfusion will not reverse
Renal clearance
- Unclear if dialyzable

**Glycoprotein IIb/IIIa Reversal**

No evidence based recommendations
2 units platelets most commonly used strategy

**Low Molecular Weight Heparin**

Typical half-life is 12 hours
Unless in renal failure
- CrCl < 30
  - half-life doubled
Recommendation is to use one half typical dose in renal dysfunction

**LMWH monitoring**

PTT not useful
Anti-factor Xa assay
- not available every place
- does not account for all the anticoagulant activity of LMWH
## LMWH antidotes

No evidence based recommendations

**Protamine**

**DDAVP**

25 mcg IV
can give every 12 hours
tachyphlaxsis at 6 doses

## Protamine and LMWH

Protamine completely neutralizes the antithrombin activity of LMWH but not the all of the anti-Xa activity

1 mg protamine for every 100 units anti-Xa activity

- enoxaparin (Lovenox) 1 mg = 100 anti-Xa units

May repeat half the dose if bleeding continues

## Protamine Toxicity

Is a weak anticoagulant

- Given repeat dose once the initial heparin has been reversed will result in more bleeding

Does cause hypotension and bradycardia

- Give slow
- Calcium helps

Can cause anaphylaxis

## Heparin

Unfractionated heparin (UFH)

Most bleeding occurs with appropriate administration of heparin with PTT in the therapeutic range

Half-life is 90 minutes

- Do not have to treat the bolus of heparin if bolus is over 2 hours ago

## Heparin Reversal = Protamine

Dose 1 mg IV per 100 units of UFH

Bolus of 5000 units within the last 2 hours = 50 mg of protamine

Infusion of 1250 u/hr = 25 mg of protamine

- 1250/h x 2 hours = dose of 2500

May check PTT to confirm reversal

May repeat dose if PTT still elevated

## Protamine Toxicity

Is a weak anticoagulant

- Given repeat dose once the initial heparin has been reversed will result in more bleeding

Does cause hypotension and bradycardia

- Give slow
- Calcium helps

Can cause anaphylaxis
Coagulopathies associated with disease states
Liver disease
Uremia
DIC

Liver disease
Vitamin K as in coumadin
2-4 units FFP
Do not expect INR to completely correct

Uremic platelet dysfunction
Platelet transfusion does not work
Mechanism of dysfunction
von Willebrand factor dysfunction
DDAVP
Cryoprecipitate
Acute hemodialysis

DIC
Factor replacement if bleeding occurs
Platelets if count low
FFP if PT/INR high
Cryoprecipitate if fibrinogen low
typically keep fibrinogen > 150 k

Questions