Reversal Options for the NOACs and Warfarin

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Do We Need Rapid Reversal?

- In most cases the anticoagulation effects wear-off within a few hours
  - About 60-65% of anticoagulation effects resolves in 2 half-lives (18-24 hours)
  - 95% will be gone by 4 half-lives (40-48 hours in most cases)
  - So just doing nothing will lead to improvement in coagulation status in many patients

Circumstances Mandating Immediate Reversal

- Intracerebral hemorrhage
- Intraventricular hemorrhage
- Major GI hemorrhage
- Major systemic hemorrhage (retroperitoneal, pericardial)
- After major trauma
- Requirement for immediate surgery

Reversal for Warfarin

- Fresh frozen plasma
  - Extensive clinical experience
  - Can take > 12 hours to have an effect
  - Risk of CHF
  - Risk of infection
  - Not recommended in many NEW guidelines

Newer Options for Warfarin Reversal

- Prothrombin Complex Concentrate (PCC)
- Various types
- Can be rapidly infused (typically 2-5 minutes)
- Reverses coagulopathy within 5-10 minutes in most cases
- Rarely needs to be re-infused
- Now recommended in most guidelines
- No clear outcome data

PCC Details

	Origin	Components	Half-life
3-factor PCC	Homologous plasma proteins	FII, FIX, FX	FII = 50-60 h, FIX = 12-30 h, FX = 40-60 h
4-factor PCC	Homologous plasma protcins	FII, FVII, FIX, FX, protcins C and S	FII = 50-60 h, FVII = 4 h, FIX = 12-30 h, FX = 40-60 h, protein C = 47 h, protein S = 49 h
aPCC (FEIBA)	Homologous plasma proteins	FIIa, FIXa, FXa, FVIIa	-
rFVIIa	Genetic engineering	rFVIIa	3.9-6.0 hours
FXa-GLAless	Genetic engineering	FXa missing Gla residues in Gla domains	-
PRT064445	Genetic engineering	FXa without Gla domain and inactivating mutation at S419	-

Capodanno et al; Recent Patents on Cardiovascular Drug Discovery, 2013

PCC vs FFP for Warfarin Reversal

- Phase III randomized, open label trial
- 4 factor PCC vs FFP
- 216 patients with active bleeding
- 69 centers involved
- All patients received vitamin K also
- Co-primary endpoints:
  - Effective hemostasis
  - INR <=1.3 within 30 minutes of Rx

Sarode et al., Circulation, 2013

Results

- TIME to complete treatment
  - PCC = 17 minutes
  - FFP = 148 minutes
- Infusion volume
  - PCC = 99 ml
  - FFP = 813 ml
- Effective hemostasis within 24 hours
  - PCC = 72%
  - FFP = 65%

More Results

- INR 1.3 or less within 30 min of end of infusion
  - PCC = 62%
  - FFP = 10%
- Treatment AEs
  - PCC = 10%
  - FFP = 21%
- Thromboembolic events
  - PCC = 7.8%
  - FFP = 6.4%

Take Home Message

- PCC, compared to FFP, provides more rapid and effective hemostasis
- PCC is well tolerated
- Treatment complications are comparable
- PCC is supported in all recent guidelines as the preferred agent to correct warfarin coagulopathies

What to do about bleeding with NOACs?

- Stop the NOAC
- Short half-life
- Keep patient well hydrated
- Correct any other abnormalities
- Supportive care
- Understand bleeding reason and source

PRT 4445
Andexanet alfa
Factor Xa Inhibitor Antidote

Recombinant Factor Xa decoy

Sequesters direct and indirect FXa inhibitors

PRT 4445

- Phase 2 trials with Rivaroxaban and Apixaban
- > 80 normal volunteers
- Short term and sustained reversal of anticoagulant effects
- No thrombotic or ischemic complications reported

Portola Web Site, accessed 2/25/14

aDabi-Fab

- Antibody fragment directed again Dabigatran
- Mimics thrombin but has **350 x** the affinity for Dabigatran
- Neutralizes dabigatran; allows thrombin to function normally
- Works within about 1 minute
- Sustained effects even with continuous Dabigatran infusions

Clinical Results

- Randomized, DB, placebo trials
- 145 healthy volunteers
- 4 gm to 8 gm IV infusions
- Dabigatran 220 mg BID
- TT, DTI, PTT, ECT, ACT assays
- Reversal of anticoagulation after 5 min infusion
- Complete and sustained reversal in all patients Rx with 4 gm

AHA 2013 Scientific Sessions, Dallas, TX

PER 977

- Synthetic molecule
- Binds both DTIs and factor Xa inhibitors
- Phase I studies
- Rapid action (complete reversal within 30 minutes)
- Studied in animals and ex-vivo human studies
- Seems to work on all NOACs

Conclusions

- There are a number of promising reversal compounds for DTIs and FXa inhibitors
- FDA has given these agents a fast-track approval process
- Best guess is that one or more may be available in the next 12-18 months barring any unexpected results

Implications

- One major barrier to avoiding the use of the NOACs will be removed
- Education about reversal will still be widely needed
- Close monitoring for ischemic complications will be needed with wide use
- There are no ischemic events with the high morbidity and mortality of an ICH—so use of NOAC reversal agents seem to justify the risk (if any)