

Prothrombin Complex Concentrates (PCCs) for PharmDs

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How did we reverse anticoagulation before the invention of PCC?

- The only oral anticoagulant was warfarin
- Reversal was fairly simple: Vitamin K +/- fresh frozen plasma (FFP)

What are limitations with using FFP as a reversal agent?

- It is less expensive than PCC but:
 - Not as good of a reversal agent compared to PCC
 - Doesn't last as long as PCC
 - Doesn't reverse the INR as well as PCC
 - FFP has an intrinsic INR of 1.6
 - The more FFP you give, the less INR reduction you get
 - Delays to administration due to:
 - Type and screen since FFP is a blood product
 - Time to thaw the FFP (fresh frozen plasma is actually frozen!)
 - Risk for volume overload and more serious complications including TACO and TRALI
 - Infectious concerns

What is a brief history of PCC?

- 3-factor PCC (Factor II, IX, and X) originally approved for Hemophilia B (Christmas Disease) a Factor IX deficiency
- First off-label use of PCC for warfarin reversal in 1997
 - 3-factor PCC + recombinant Factor VII
 - 25-50 units/kg PCC v. FFP
 - Post-INR 1.3 v. 2.3
 - FFP had higher baseline INR
- Then the 4-factor PCC (Factor II, VII, IX, and X) products were introduced

- Kcentra – Approved in 2013 for warfarin reversal
- FEIBA – Approved in 2000s
 - First FEIBA study for anticoagulation reversal was in 2005
 - Used prior to Kcentra being introduced

Any current role for the use of 3-factor PCC products with the invention of 4-factor PCC products?

- 2016 Guidelines for Reversal of Antithrombotics in Intracranial Hemorrhage
 - Endorsed by Neurocritical Care Society and Society of Critical Care Medicine
 - “Suggest using 4-factor PCC over 3-factor PCC”
 - Mostly due to having more and better evidence
 - 4-factor PCC contains Factor VII which has theoretical hemostatic benefits
 - Older evidence suggested superiority of 4-factor PCC products
 - Newer evidence hasn’t shown a difference comparing 3-factor to 4-factor products
 - But the majority of providers still use 4-factor PCC products based on the above

When should we be using PCC? Anyone who is bleeding/needs reversal of their anticoagulation?

- Big role for Pharmacists to practice “Factor Stewardship” and ensure appropriate use of these agents
 - Because they are not without risks themselves
- Reserve PCC for patients presenting with life-threatening bleeding
 - Not for the “stable” GI bleed patient
- Emergent surgical case
 - Talk with Attendings on when the case is scheduled
 - Be sure to time the administration appropriately based on the time of surgery
 - Can potentially wait it out and avoid using PCC for reversal
- For non-life-threatening cases, FFP may be a less expensive option for warfarin reversal

- Delays in time and other limitations aren't as harmful since it's not life-threatening
- Hard to argue not administering PCC for bleeding due to a DOAC (no real alternate agent), however it's always worth having a discussion.
 - Will depend on the case
 - Because the other option is just wait, which is less ideal in an emergent setting
- Always worth having a discussion with the team

What is the role of PCC for non-reversal indications such as coagulopathy due to trauma or cirrhosis?

- Cirrhosis
 - Local hospital protocol: 1000 unit 4-factor PCC
 - May administer PCC +/- IV Vitamin K
 - May give both (PCC works now, Vitamin K works in 4-6 hours)
 - When administering FFP to patients in cirrhosis, a 2019 study showed that only 1/52 patients had an actual improvement in their endogenous thrombin potential
 - 1/3 of patients also showed worsening thrombin generation post-FFP
 - Unsure if this means providers will want to use more PCC in patients with cirrhosis, since this may mean less FFP
- Trauma
 - Looking for more human data but more is being published, because PCC is being used more in trauma
 - Early studies (2012 and 2014 by Joseph et al) used 25 unit/kg 3-factor PCC
 - Reduced blood product administration
 - Faster time to INR correction
 - 2018 study (Jehan, et al) looked at 4-factor PCC
 - Reduced transfusion requirements
 - Improved time to INR correction
 - Lowered mortality
 - Unfortunately, no information on PCC dosing used

- Recommend 25 units/kg 4-factor PCC dose for trauma-induced coagulopathy
 - Generally speaking, this is ~1500 units
 - FFP has approximately 250 units Factor IX equivalents in each unit
 - 1500 units of PCC would approximately equal 6 units FFP which is a reasonable starting place in these patients
- Don't want PCC to replace all FFP, just reduce the number of units needed (the trauma patients will likely need the volume from FFP)

What is your standard Kcentra (4-factor PCC) fixed dosing strategy?

- 1500 unit Kcentra fixed dose protocol
 - Most of the published fixed dose Kcentra literature just has one standard dose
- Scott's hospital protocol is unique:
 - Increase fixed dose to 2000 unit Kcentra if:
 - TBW > 100 kg
 - Based on Klein et al post-hot analysis showing higher failure rate if patient weight > 95 kg
 - Baseline INR > 7.5
 - Based on two studies:
 - Klein et al demonstrated 10 times higher failure rate if baseline INR > 10
 - Khorsand et al demonstrated less likely to reach target INR if baseline INR > 7.5
 - Intracranial hemorrhage on presentation
 - Cooperation with neurology team to reduce the theoretical risk of PCC failure for ICH patients

What are some advantages to using a Kcentra fixed dose strategy?

- Cost savings
 - 3-4 studies have shown ~ \$1000/dose cost savings by using a fixed dose protocol compared to standard weight based Kcentra dosing

- Easier dosing strategy
- Reduced time to administration
 - Don't have to wait for a baseline INR
- Lower risk of thromboembolic complications
 - Zemrak et al found ~15% complication rate if receiving 35-50 unit/kg Kcentra compared to 0% for patients receiving 15-25 unit/kg Kcentra

When do you re-dose PCC? Based on laboratory findings only or clinical findings as well?

- Likely is a combination of both, can't use just one in isolation
 - Could argue administering an additional fixed dose of Kcentra if the ICH is expanding on imaging but the INR is at goal
 - But unsure on dose to recommend (1000 units Kcentra?)
 - Could increase risk of thromboembolic complications
 - Additionally, INR may be above goal but hemostasis has been achieved on CT so no further Kcentra doses may be needed
 - Real-world TEG analysis may help guide this in the future
- INR is re-checked 30 minutes post-Kcentra administration
 - Realistically happens 45-60 minutes after typically
 - Can be drawn too soon and don't see effects of PCC administration, potentially leading to unnecessary additional administration

Does your management of patients change for patients who present with an INR < 2 with an indication for anticoagulation reversal?

- More off-label use
- 15 unit/kg Kcentra based on Zemrak et al study in patients with ICH & INR < 2
 - 95% effective at achieving INR < 1.5
 - Scott calculates 15 unit/kg v. fixed dose protocol (2000 unit Kcentra)
 - Picks the lower dose to administer
- For patients presenting with an INR < 2 and no ICH, have a discussion with the team
 - The patient may not need urgent reversal with PCC

What do the guidelines recommend in regard to reversal of antithrombotics with Kcentra?

- 2016 Guideline for Reversal of Antithrombotics in Intracranial Hemorrhage
 - Strong recommendation for weight-based Kcentra dosing (mod. QOE)
- 2017 ACC Consensus on Management of Bleeding on Oral Anticoagulants
 - Suggest both fixed- and weight-based Kcentra dosing option
 - They recommend 1000 unit fixed dose Kcentra for “any bleed” and 1500 units for ICH
 - 1000 unit fixed dose Kcentra has been linked to a higher failure rate especially in patients with a higher baseline INR or higher admission weight
 - Fixed dose Kcentra should likely be at least 1500 units to reduce failure
 - In line with recently published studies regarding fixed-dose Kcentra
- PROPER3 study will help provide some clarity
 - Comparing 1000 unit fixed-dose PCC v. weight-based PCC

How does Kcentra (4-factor PCC) differ from FEIBA (4-factor activated PCC)?

- Both are 4-factor PCC (II, VII, IX, and X)
- Kcentra – all factors are in the inactivated form
- FEIBA – Factor VII is in the activated form
 - FEIBA is more potent
 - Fixed dose is 500-1000 unit FEIBA
 - Lower fixed dose compared to Kcentra fixed doses (1500-2000 units) but similar efficacy for INR reductions
 - No difference in clinical outcomes using FEIBA compared to Kcentra

What is the general dosing strategy for FEIBA when reversing anticoagulation?

- Depends on what anticoagulant you are looking to reverse
 - Warfarin

- 500 units FEIBA
- If INR >5: 1000 units FEIBA
- DOAC
 - Less clear
 - Dose ranges from 10-50 unit/kg

Should we be using Kcentra for DOAC reversal and if so, what should our dosing strategy be?

- 4 studies looking at this exact question
 - Majeed et al
 - Largest of the studies (84 patients)
 - 1500-2000 unit Kcentra (~25 unit/kg)
 - ~70% presented with ICH
 - Hemostatic efficacy 69%
 - Schulman et al
 - 66 patients; 54% presenting with ICH
 - 2000 unit Kcentra (~25 unit/kg)
 - Hemostatic efficacy 68%
 - Smith et al
 - 31 patients with >50% presenting with ICH
 - Dosing ranged from 25-50 unit/kg
 - 38% received 25 unit/kg
 - 2 failures were not dose related
 - Hemostatic efficacy 81%
 - Berger et al
 - 22 patients all with ICH
 - 25 unit/kg Kcentra
 - Hemostatic efficacy 95%
- Overall the hemostatic efficacy seems to be ~70-80% with Kcentra for DOAC reversal
 - This seems to be the range of efficacy for all the reversal agents we use
 - Study that gained FDA approval for Kcentra showed an efficacy of ~70%
 - No current agent is 100% effective

What is the role for FEIBA in reversal of DOAC?

- Less evidence with FEIBA compared to Kcentra for DOAC reversal
 - 3 main studies to discuss
 - Dibu et al
 - 5 ICH patients all received 50 unit/kg FEIBA
 - 100% hemostatic efficacy
 - Mao et al
 - 11 ICH patients received 20 unit/kg FEIBA
 - Hemostatic efficacy ~55%
 - Dager et al
 - 64 patients received low dose (10 unit/kg FEIBA) or moderate (25 unit/kg FEIBA)
 - Hemostatic efficacy ~97% (2/64 patients)
 - Largest study published so far
 - Less data, less patients, large variability in efficacy and dosing for FEIBA
- If you are using FEIBA for reversal, consider using 25 units/kg

Is there a preferred agent, Kcentra or FEIBA, when reversing DOAC?

- 2016 Guideline for Reversal of Antithrombotics in Intracranial Hemorrhage
 - Don't list a preference for either Kcentra or FEIBA (both dosed at 50 unit/kg)
- Scott prefers Kcentra at a dose of 25 unit/kg based on available evidence
- If your hospital uses FEIBA, more unsure on what to do
 - 25 unit/kg FEIBA is probably okay but just much less evidence

Is there a preference for Kcentra or FEIBA for the reversal of warfarin?

- Retrospective review comparing standard dose KCentra v. fixed dose FEIBA
 - No difference found in ability to target INR < 1.4
 - 77% in FEIBA group, 67% in Kcentra group
 - Efficacy found mirrored other published studies, but smaller study
 - Study done in collaboration with Shaun Rowe

- PCCWAR (2018 ACCP Poster Presentation)
 - 6 sites with 3 treatment arms
 - Fixed dose FEIBA vs. Standard dose Kcentra vs. Fixed dose Kcentra
 - Initial data analysis showed that standard-dose Kcentra more efficacious (INR goal ≤ 1.4) than either arm
 - Standard dose Kcentra ~77% efficacious
 - ~55% for other treatment arms
 - However, standard dose Kcentra group had a significantly lower baseline INR than other groups
 - May have contributed to the difference found

Should we be trying to have both 4-factor PCC products (Kcentra and FEIBA) on formulary?

- Scott doesn't think so
 - This isn't a situation where one agent is clearly superior
- If you happen to have both agents on formulary, might preferentially use Kcentra since it has more published data
 - Better data with DOAC reversal and similar data with warfarin reversal

Preferred dosing for FEIBA and its use in DOAC reversal, fixed dose or weight-based dosing?

- Weight-based dosing for DOAC reversal is much more common
 - But that dose varies from 10-50 units/kg
- Would use weight-based for now based on the available literature
 - 10-25 unit/kg FEIBA
 - Anecdotally, some hospitals use 1500 unit FEIBA
 - Less literature to guide this dosing strategy

Current role for Andexxa (andexanet alfa) for the reversal of Factor Xa inhibitors compared to 4-factor PCC products?

- Pros:
 - Only “agent specific” DOAC reversal currently available
 - High degree of drug binding while Andexxa is infusing which results in a rapid acting anti-Xa activity decrease
 - Rapid acting
 - Anti-Xa activity falls to almost zero
- Cons:
 - Lack of clear outcome data from ANNEXA-4 study
 - Lots of exclusions (e.g. pre-surgery), hard to extrapolate the findings
 - PK/PD of the drug isn’t great
 - As soon as you turn the infusion off, the effects wear off quickly (back to baseline anticoagulation levels in 1-2 hours)
 - Cost

4-Factor PCC compared to Andexxa for Factor Xa inhibitor reversal?

- At this point, there is data to support giving Kcentra (4-factor PCC) as opposed to Andexxa for anticoagulation reversal
 - Number of unique studies, amount of patients, consistency of results
 - May be as good if not better

Would we be using more Andexxa if it wasn’t for the cost?

- It all comes back to the kinetics
 - Idarucizumab completely and irreversibly binds dabigatran and eliminates it from the body
 - After discontinuation of andexanet alfa infusion, the patient essentially returns to their baseline levels of anticoagulation relatively quickly
 - Would like to see more data on the downstream effects compared to PCC

- Additionally, a recent article was published in *Neurocritical Care* which pointed out that the FDA Clinical Reviewers voted to NOT approve Andexxa as “the safety and efficacy data [were] not adequate to support” approval.
 - However, they were overruled by the Director for the Office of Tissues and Advanced Therapies and it was given approval
 - With the caveat that an RCT against the standard of care (in this case PCC) must be performed

If Scott had a life-threatening bleed on Xarelto or Eliquis, what reversal agent and dosing strategy would he want?

- Kcentra for DOAC reversal
- 25 units/kg

How can Pharmacists help with safe and effective use of PCC agents?

- *Factor Stewardship!*
 - PCCs are expensive and not without risks
 - Only use in appropriate cases
 - If it’s a surgical patient find out when the surgery is actually scheduled to administer the PCC when it’s maximally effective
 - Potentially could wait it out and not use PCC
 - Or time the administration to have its maximal benefit
 - Ensure the correct dose is ordered
 - Avoid overdosing
 - Reduce costs and possible thromboembolic complications
 - Also want to avoid underdosing for life-threatening bleeding
 - Check with the RN to ensure they don’t have any questions about administration
 - For warfarin reversal, make sure the IV Vitamin K is ordered
 - INR may rebound in 6-8 hours if not
 - But administer PCC first and Vitamin K second
 - Ensure repeat INR is ordered 30-60 minutes post-administration
 - Follow-up and be sure re-dosing isn’t needed

Take-Home Points

- Warfarin reversal
 - Fixed-dose Kcentra
 - Literature supports the lower fixed dose of Kcentra
 - 1500-2000 units
 - Scott's post on EMPHarmD for more information:
<https://empharmd.com/2017/10/26/ftfy-prothrombin-complex-concentrate-that-is/>
 - No superiority between Kcentra and FEIBA for warfarin reversal
 - If using FEIBA prefer a fixed dose of 500-1000 units
 - Administer IV vitamin K in addition to PCC
- DOAC reversal
 - Kcentra preferred to FEIBA
 - More patients, consistent data regarding efficacy
 - 25 units/kg
- Factor Stewardship
 - Making sure these therapies are being used appropriately
 - Only administer when actually needed (life-threatening bleeding)
 - Not under- or over-dosing