REVERSAL STRATEGIES OF ANTICOAGULATION THERAPIES

Nadia Awad, Pharm.D., BCPS
Clinical Assistant Professor, Emergency Medicine
Rutgers, The State University of New Jersey
Twitter: Nadia_EMPharmD
PRESENTER DISCLOSURE INFORMATION

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Reversal Strategies of Anticoagulation Therapies

FINANCIAL DISCLOSURE:
None
LEARNING OBJECTIVE

Assess the clinical evidence surrounding the use of emerging treatment strategies for the reversal of oral anticoagulant therapies
A CASCADE OF EVENTS

Intrinsic Pathway

XII → XIIa

XI → Xla

IX → IXa

X → Xa

Extrinsic Pathway

VIIa → VII

VII → X

X → Thrombin (IIa)

Platelet activation

Warfarin

Dabigatran

Rivaroxaban

Apixaban

Edoxaban

Fibrinogen

Fibrin → Clot
CONSIDERATIONS IN THE BLEEDING PATIENT
CONSIDERATIONS IN THE BLEEDING PATIENT

Severity of Bleeding and Status

Access

Necessity of Emergent Procedures

Rebound Post-Intervention
CASE I

75-year-old female with history of hypertension, congestive heart failure, and proximal deep vein thrombosis (DVT)

Presents to ED with headache and vomiting with a decreased level of consciousness

Current medications: Lisinopril, metoprolol succinate, digoxin, furosemide, isosorbide mononitrate, warfarin
WARFARIN

“Vitamin K Antagonist”

Meaning of the PT/INR

Antidotes Galore
VITAMIN K (PHYTONADIONE)

Routes of Administration (IV versus PO)

Warfarin Resistance

Anaphylactoid Reaction with IV Infusion
**VITAMIN K (PHYTONADIONE)**

<table>
<thead>
<tr>
<th>INR Value</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.5 to 10.0</td>
<td>Hold warfarin. Resume therapy when INR is therapeutic.</td>
</tr>
<tr>
<td>≥ 10.0</td>
<td>Hold warfarin. Administer vitamin K at a dose of 2.5 mg orally.</td>
</tr>
<tr>
<td>Any major bleeding</td>
<td>Hold warfarin. Administer vitamin K at a dose of 5 to 10 mg as a slow IV infusion with four-factor prothrombin complex concentrate.</td>
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Chest 2012; 141:e152S-e184S.
VITAMIN K (PHYTONADIONE)

Vitamin K Dosing to Reverse Warfarin Based on INR, Route of Administration, and Home Warfarin Dose in the Acute/Critical Care Setting

Laura V Tsu, J Erin Dienes, and William E Dager


No increase in reversal rate with vitamin K doses > 2 mg IV
BACK TO OUR PATIENT

(CT) scan of the brain: Right subdural hematoma, right temporal intraparenchymal hemorrhage, and small subarachnoid hemorrhage

INR is 3.8
WHAT INTERVENTIONS WILL YOU RECOMMEND AT THIS TIME?

1. Vitamin K 10 mg IV infusion x 1 dose
2. FFP 15 U/kg x 1 dose
3. 4-Factor PCC 25 U/kg x 1 dose
4. A & B
5. A & C
FRESH FROZEN PLASMA (FFP)

Clotting Proteins

ABO Matching

Correction: 1 Unit (250 mL) = 2.5 to 5% of Factors

Initial Dose: 15 mL/kg (4 Units)

“INR of FFP”

Volume Resuscitation in the Bleeding Patient
LIMITATIONS OF FFP

Volume

Thawing Time

Viral Transmission

Transfusion Reactions
PROTHROMBIN COMPLEX CONCENTRATE (PCC)
GRADE 2C RECOMMENDATION

For patients with VKA-associated major bleeding, we suggest rapid reversal of anticoagulation with four-factor prothrombin complex concentrate rather than with [fresh frozen] plasma.
4-FACTOR PROTHROMBIN COMPLEX CONCENTRATE (PCC)

Kcentra: April 2013

Factor IX-Based Dosing

<table>
<thead>
<tr>
<th>Initial INR</th>
<th>INR 2 to &lt; 4</th>
<th>INR 4 to &lt; 6</th>
<th>INR &gt; 6</th>
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<tbody>
<tr>
<td>Dose</td>
<td>25 Units/kg</td>
<td>35 Units/kg</td>
<td>50 Units/kg</td>
</tr>
<tr>
<td></td>
<td>Maximum: 2500 U</td>
<td>Maximum: 3500 U</td>
<td>Maximum: 5000 U</td>
</tr>
<tr>
<td></td>
<td>Administer with vitamin K 10 mg IV x 1 over 30 minutes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PCCS HAVE BEEN SHOWN TO BE SUPERIOR THAN FFP IN IMPROVING PATIENT-RELATED OUTCOMES WHEN USED FOR ANTICOAGULANT REVERSAL.

1. True
2. False
HEAD TO HEAD

FFP | PCC
TRIAL LEADING TO FDA APPROVAL

Efficacy and Safety of a 4-Factor Prothrombin Complex Concentrate in Patients on Vitamin K Antagonists Presenting With Major Bleeding
A Randomized, Plasma-Controlled, Phase IIIb Study

Ravi Sarode, MD; Truman J. Milling Jr, MD; Majed A. Refaai, MD; Antoinette Mangione, MD, PharmD; Astrid Schneider, PhD; Billie L. Durn, BS; Joshua N. Goldstein, MD, PhD

TRIAL LEADING TO FDA APPROVAL

INR Correction After 30 Minutes:
4-Factor PCC Superior to FFP
(62.2% versus 9.6%)

24-Hour Efficacy:
4-Factor PCC Non-Inferior to FFP
(72.4% versus 65.4%)

Thromboembolic Events:
7.8% with PCC versus 6.4% with FFP
SURROGATE ENDPOINTS = OUTCOMES?

Mortality in vitamin K antagonist-related intracerebral bleeding treated with plasma or 4-factor prothrombin complex concentrate

Ammar Majeed¹; Karina Meijer²; Ramiro Larrazabal³; Fabian Arnberg⁴; Gert J. Luijckx⁵; Robin S. Roberts⁶,⁸; Sam Schulman¹,⁷,⁸

Thromb Haemost 2014; 111: 233–239

No difference in 30-day mortality
FACTOR EIGHT INHIBITOR BYPASS ACTIVITY (FEIBA)

Activated PCC (aPCC)

Clinical Evidence

Risk of Thromboembolic Complications

RECOMBINANT FACTOR VIIA (RFVIIA)

Most Pronounced Clotting Ability

Rapid INR Correction

Risk of Thromboembolic Events

Lack of Survival Benefit

Correction of Coagulopathy?

Consensus: Not Recommended
CASE II

63-year-old female with a past medical history significant for atrial fibrillation and early-onset Alzheimer’s disease

Presents to ED after inadvertently overdosing on home medications

Current medications include dabigatran 150 mg PO BID and memantine

Vital signs:
85/40 | 110 | 24 | 95% O₂ sat RA
WHICH OF THE FOLLOWING LABORATORY TESTS WILL NOT PROVIDE ADDITIONAL INFORMATION RELEVANT TO THIS CASE?

1. Thrombin time
2. Chromogenic anti-factor Xa assay
3. Serum creatinine
4. Ecarin clotting time
DABIGATRAN

Direct Thrombin Inhibitor

No Antidote

Limited Data for Reversal
LABORATORY ASSAYS FOR DABIGATRAN

Presence:
Thrombin Time (TT)

Quantitative:
Dilute Thrombin Time (dTT)
Ecarin Clotting Time (ECT)

Sensitivity:
Activated Partial Thromboplastin Time (aPTT)

Thromb Haemost 2010; 103:1116-1127.
Am J Hematol 2012; 87:S141-S145.
REVERSAL OF DABIGATRAN

FFP: No Likely Benefit

rVIIa: Suggested Antagonism

PCC: Mixed Data

aPCC: Potential Benefit

Thromb Haemost 2010; 103:1116-1127.
Am J Hematol 2012; 87:S141-S145.
After a series of diagnostic tests are performed, an upper gastrointestinal bleed is confirmed.

Laboratory parameters:
- SCr 2.0 mg/dL
- Thrombin Time = 98 s
HEMODIALYSIS SHOULD BE INITIATED AT THIS TIME.

1. True
2. False
RENAL REPLACEMENT THERAPY FOR DABIGATRAN

Ideal Pharmacokinetic Properties

Logistics

Rebound Phenomenon:
Four Published Case Reports

Monitoring Post-Intervention?

J Med Toxicol 2014 Jan 3 [Epub ahead of print].
RIVAROXABAN

Factor Xa Inhibitor

No Antidote

Limited Data on Reversal
LABORATORY ASSAYS FOR RIVAROXABAN

Presence:
Chromogenic Anti-Factor Xa

Quantitative:
Chromogenic Anti-Factor Xa
Dilute Prothrombin Time (dPT)

Sensitivity:
Prothrombin Time (PT)
Prothrombinase-Induced Clotting Time (PiCT)

Thromb Haemost 2010; 103:1116-1127.
Am J Hematol 2012; 87:S141-S145.
REVERSAL OF RIVAROXABAN

FFP: Possible Benefit

rVIIa, PCC, aPCC: Mixed Data

Renal Replacement Therapy: No Likely Benefit

Thromb Haemost 2010; 103:1116-1127.
Am J Hematol 2012; 87:S141-S145.
APIXABAN

Factor Xa Inhibitor

No Antidote

Limited Data on Reversal
REVERSAL OF APIXABAN: NEW DATA

Reversal of Apixaban Induced Alterations in Hemostasis by Different Coagulation Factor Concentrates: Significance of Studies In Vitro with Circulating Human Blood

Gines Escolar¹*, Victor Fernandez-Gallego²*, Eduardo Arellano-Rodrigo¹, Jaume Roquer³, Joan Carles Reverter¹, Victoria Veronica Sanz¹, Patricia Molina¹, Irene Lopez-Vilchez¹, Maribel Diaz-Ricart¹, Ana Maria Galan¹

Correction in prolonged clotting time:
\[ rFVIIa \geq aPCC > PCC \]

Thrombin generation:
\[ PCC \geq aPCC > rFVIIa \]

GENERAL RECOMMENDATION

KEEP CALM AND CALL YOUR PHARMACIST
REVERSAL STRATEGIES OF ANTICOAGULATION THERAPIES

Nadia Awad, Pharm.D., BCPS
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Rutgers, The State University of New Jersey
Twitter: Nadia_EMPharmD