The Thin Line Between Reversal and Management: The DOAC's

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Disclosure

I have no relevant financial relationships with the manufacturer(s) of any commercial product(s) and/or provider(s) of commercial services discussed in this CME activity.

I do intend to discuss an unapproved/investigative use of a commercial product/device in my presentation.
Objectives

1. Review the DOAC’s and their pharmacologic effect on the coagulation cascade.
2. Review the reversal strategies for this class of medications.
   2a. When is aggressive reversal required?
3. Apply this new information to your everyday practice.
An evidence informed approach to emergent oral anticoagulant reversal
Earlier Today

⚠️ EMERGENCY ALERTS

Emergency Alert
BALLISTIC MISSILE THREAT INBOUND TO HAWAII. SEEK IMMEDIATE SHELTER. THIS IS NOT A DRILL.
Objectives

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Warfarin
Dabigatran
Apixaban
Rivaroxaban
Edoxaban
Direct Oral Anticoagulants in the Coagulation Cascade

Intrinsic Pathway

Extrinsic Pathway

Warfarin

Rivaroxaban
Apixaban
Edoxaban

Factor Xa

Prothrombin (Factor II)

Thrombin (Factor II)

Fibrinogen

Fibrin

Fibrin clot

Dabigatran
<table>
<thead>
<tr>
<th>Drug</th>
<th>PT/INR</th>
<th>aPTT</th>
<th>Half Life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>Increased</td>
<td>No impact</td>
<td>Days</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>IF ELEVATED, SUGGESTS DABIGATRAN PRESENT AT 3-4X THERAPEUTIC CONCENTRATION</td>
<td>ELEVATED IF PRESENT AT THERAPEUTIC CONCENTRATIONS (1.5 control at 12 hours)</td>
<td>12-17 hours</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>INCREASED AT THERAPEUTIC CONCENTRATIONS*</td>
<td>PROLONGED IF PRESENT AT SUPRATHERAPEUTIC LEVELS*</td>
<td>5-9 hours</td>
</tr>
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</tr>
<tr>
<td>Edoxaban</td>
<td>INCREASED AT THERAPEUTIC CONCENTRATIONS*</td>
<td>PROLONGED IF PRESENT AT SUPRATHERAPEUTIC LEVELS*</td>
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Warfarin
Dabigatran
Apixaban
Rivaroxaban
Edoxaban
Phytonadione (Vitamin K)

10mg IV
4 Factor Prothrombin Complex Concentrate

Max 50 units/kg*
Max Dose 5000 units

* [http://www.kcentra.com/dosage-calculator](http://www.kcentra.com/dosage-calculator) for INR based dosing
<table>
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<tr>
<th>Parameter</th>
<th>PCC</th>
<th>FFP</th>
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<tbody>
<tr>
<td>Cost</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Time to normalization of INR</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Volume</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Guidelines</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Thrombotic Events</td>
<td>~</td>
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Dabigatran
Apixaban
Rivaroxaban
Edoxaban
Direct Oral Anticoagulants in the Coagulation Cascade

- Intrinsic Pathway
- Extrinsic Pathway

- Warfarin
- Rivaroxaban
- Apixaban
- Edoxaban
- Dabigatran

- Prothrombin (Factor II)
- Thrombin (Factor II)
- Fibrinogen
- Fibrin
- Fibrin clot
IDARUCIZUMAB
2.5g IV x 2 doses not more than 15 minutes apart
Idarucizumab

Fab binds dabigatran with 350x affinity for thrombin

Rapid onset

Industry funded trial without a control group with 25% adverse event rate and ~5% thrombosis rate
Warfarin
Dabigatran
ApiXaban
Rivaroxaban
Edoxaban
Direct Oral Anticoagulants in the Coagulation Cascade

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Factor Xa

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Thrombin (Factor II)

Dabigatran

Fibrinogen

Fibrin

Fibrin clot
ACTIVATED CHARCOAL MERCK
U.S.P.
ALSO FOR DECOLORIZING
1 lb.

Merck & Co. Inc.
Manufacturing Chemists
Rahway, N.J.

Printed in U.S.A.
ANDEXANET ALFA

Binds and sequesters Xa inhibitors

Rapid onset

Anti-factor Xa activity increases to placebo levels within 2 hours
<table>
<thead>
<tr>
<th>FXa Inhibitor</th>
<th>FXa Inhibitor Last Dose</th>
<th>Timing of FXa Inhibitor Last Dose Before Andexanet alfa Initiation</th>
</tr>
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<tbody>
<tr>
<td>Apixaban</td>
<td>≤5 mg</td>
<td>Low dose</td>
</tr>
<tr>
<td></td>
<td>&gt;5 mg or unknown</td>
<td>High dose</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>≤10 mg</td>
<td>Low dose</td>
</tr>
<tr>
<td></td>
<td>&gt;10 mg or unknown</td>
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Andexanet Alfa Dosing

Low dose: 400 mg IV bolus administered at a rate of ~30 mg/minute, followed within 2 minutes by an IV infusion of 4 mg/minute for up to 120 minutes

$400 \text{mg} + 480 \text{mg} = 880 \text{mg}$

High dose: 800 mg IV bolus administered at a rate of ~30 mg/minute, followed within 2 minutes by an IV infusion of 8 mg/minute for up to 120 minutes

$800 \text{mg} + 960 \text{mg} = 1760 \text{mg}$
$30K-$60K
Full Study Report of Andexanet Alfa for Bleeding Associated with Factor Xa Inhibitors


Andexanet Alfa: More garbage science in the New England Journal of Medicine
4 Factor Prothrombin Complex Concentrate

50 units/kg

Max Dose 5000 units
Ciraparantag
Warfarin
Dabigatran
Apixaban
Rivaroxaban
Edoxaban
References


References


