Ask the Experts: Developing a Systems Approach for Managing Reversal of Oral Anticoagulant Therapy

Presented as a Live Webinar
Wednesday, March 20, 2013
1:00 p.m. – 2:00 p.m. EDT

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WEBINAR INFORMATION

How do I register?
Go to http://ashpadvantage.com/reversal/experts.html and click on the Register button. After you submit your information, you will be e-mailed computer and audio information.

What is a live webinar?
A live webinar brings the presentation to you – at your work place, in your home, through a staff in-service program. You listen to the speaker presentation in “real time” as you watch the slides on the screen. You will have the opportunity to ask the speaker questions at the end of the program. Please join the conference at least 5 minutes before the scheduled start time for important announcements.

How do I process my Continuing Education (CE) credit?
Continuing pharmacy education for this activity will be processed on ASHP’s new eLearning system and reported directly to CPE Monitor. After completion of the live webinar, you will process your CPE and print your statement of credit online at http://elearning.ashp.org/my-activities. To process your CPE, you will need the enrollment code that will be announced at the end of the webinar.

View full CE processing instructions

What if I would like to arrange for my colleagues to participate in this webinar as a group?
One person serving as the group coordinator should register for the webinar. That group coordinator will receive an e-mail confirmation with instructions for joining the webinar. A few minutes before the webinar begins, the group coordinator should launch the webinar link. Once the webinar has been activated, the coordinator will have the option to open the audio via VoIP (Voice Over IP) on the webinar toolbar or use a touch tone phone with the provided dial-in information. At the conclusion of the activity, the group coordinator will complete a brief online evaluation and report the number of participants at that site. Each participant will process his or her individual continuing education statement online.

What do I need in order to participate in the webinar?
1. Computer with internet access and basic system requirements. When you register, the webinar system will assess your system to ensure compatibility.
2. Telephone to dial the toll-free number and listen to the presentation (if you choose not to use Voice Over IP [VoIP] via your computer).

Webinar System Requirements
Be sure to view the webinar system requirements for Windows, Mac, iOS, and Android prior to the activity.
Ask the Experts: Developing a Systems Approach for Managing Reversal of Oral Anticoagulant Therapy

ACTIVITY FACULTY

Edith A. Nutescu, Pharm.D., FCCP
Activity Chair and Moderator
Clinical Professor
The University of Illinois at Chicago College of Pharmacy
Director, Antithrombosis Center
The University of Illinois Hospital and Health Sciences System
Chicago, Illinois

Edith A. Nutescu, Pharm.D., FCCP, is Clinical Professor in the Department of Pharmacy Practice, Department of Pharmacy Administration, and Center for Pharmacoeconomic Research at University of Illinois at Chicago College of Pharmacy. She also is Director of the Antithrombosis Center at the University of Illinois at Chicago Medical Center.

Dr. Nutescu earned her Doctor of Pharmacy degree with high honors at the University of Illinois at Chicago College of Pharmacy. After graduation, she went on to complete a pharmacy practice residency at Lutheran General Hospital–Advocate Health Care in Park Ridge, Illinois, and a primary care specialty residency at the University of Illinois at Chicago Medical Center, both accredited by the American Society of Health-System Pharmacists (ASHP).

Dr. Nutescu maintains an active clinical practice and research program. Her research and practice interests are in the areas of comparative effectiveness, health services, and outcomes, with emphasis in cardiovascular diseases, stroke, thrombosis, and antithrombotic therapies. She has authored over 100 scientific articles and book chapters, and she coauthored “Anticoagulation Therapy: A Point-of-care Guide” published by ASHP in 2011. Her research has been funded by the Department of Health and Human Services, Agency for Healthcare Research and Quality, and National Center for Research Resources. She is a recipient of the Ruth L. Kirchstein National Research Service Award for 2010-2012. She has lectured extensively both nationally and internationally on topics related to thrombosis, antithrombotic therapies, cardiovascular diseases, and stroke.

Dr. Nutescu serves on the editorial boards for Pharmacotherapy, Annals of Pharmacotherapy, and Thrombosis, and she previously was on the editorial board for the American Journal of Health-System Pharmacy. Dr. Nutescu is active in several professional organizations, and she currently is a member of the Board of Regents for the American College of Clinical Pharmacy (ACCP), Board of Directors for Pharmacotherapy, and Board of Directors of the Anticoagulation Forum. She has served on the Oral Anticoagulant National Advisory Board of the National Consumers League Senior Outpatient Medication Safety Coalition and was the only pharmacist member nominated to serve on the steering committee of the National Quality Forum and The Joint Commission that developed “National Consensus Standards for the Prevention and Care of Venous Thrombosis.” Dr. Nutescu has been recognized as a fellow of ACCP and is the recipient of the ACCP 2009 Clinical Practice Award and ASHP Section of Home and Ambulatory Care Practitioners 2010 Distinguished Service Award.
William E. Dager, Pharm.D., BCPS (AQ-Cardiology)
Pharmacist Specialist
UC Davis Medical Center
Sacramento, California

William E. Dager, Pharm.D., BCPS (AQ-Cardiology), is a pharmacist specialist at UC Davis Medical Center in Sacramento, California, where he is responsible for managing challenging cases in anticoagulation, pharmacokinetics, and critical care. He also is clinically active with the cardiology service and serves as the director of the postgraduate year two (PGY-2) residency in cardiology at UC Davis. In addition, Dr. Dager holds three academic positions. He is Clinical Professor of Pharmacy at the University of California, San Francisco (UCSF) School of Pharmacy and Clinical Professor of Medicine at the University of California, Davis (UC Davis) School of Medicine. He also serves as Clinical Professor at the Touro School of Pharmacy in Vallejo, California.

Dr. Dager earned his Doctor of Pharmacy degree at UCSF and completed a residency at the UC Davis Medical Center in Sacramento. In addition, he completed the University of Pittsburgh Nephrology Pharmaceutical Care Preceptorship. He is a board-certified pharmacotherapy specialist and fellow of the American College of Clinical Pharmacy (ACCP), American Society of Health-System Pharmacists (ASHP), California Society of Hospital Pharmacists, and Society of Critical Care Medicine (SCCM).

Dr. Dager's research interests focus on anticoagulation, critical care medicine, cardiovascular disease, and pharmacokinetics and pharmacodynamics. He has authored numerous articles, book chapters, and scientific reviews, and he coauthored “Anticoagulation Therapy: A Point-of-care Guide” published by ASHP in 2011. He also regularly makes presentations at national and international educational conferences.

Dr. Dager serves as a reviewer and editorial board member for several medical journals, and he currently is chair of the Editorial Advisory Board Panel on Anticoagulation for The Annals of Pharmacotherapy. He has served as a site coordinator for the ASHP Research and Education Foundation Antithrombotic Pharmacotherapy Traineeship.

Dr. Dager has received multiple teaching and professional awards, including the 2008 ACCP Best Practice Award.
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The faculty and planners report the following relationships:

Edith A. Nutescu, Pharm.D., FCCP, Activity Chair

Dr. Nutescu declares that she has served as a consultant for Daiichi-Sankyo Inc. and received a research grant and served as a consultant for Janssen Pharmaceuticals, Inc.

William E. Dager, Pharm.D., BCPS (AQ-Cardiology)

Dr. Dager declares that he has no relationships pertinent to this activity.

Susan R. Dombrowski, M.S., B.S.Pharm.

Ms. Dombrowski declares that she has no relationships pertinent to this activity.

Carla J. Brink, M.S., B.S.Pharm.

Ms. Brink declares that she has no relationships pertinent to this activity.

ASHP staff has no relevant financial relationships to disclose.
ACTIVITY OVERVIEW

This activity will provide health-system pharmacists with a foundation for developing a systems approach for reversing oral anticoagulant therapy given the paucity of data available. The faculty will also offer clinical pearls related to the dosing and timing of agents used to reverse oral anticoagulant therapy.

The content for this live webinar is based on questions raised by participants in a recent educational symposium on this topic. Time for questions and answers from the webinar audience will be provided at the end of the presentation.

LEARNING OBJECTIVES

At the conclusion of this application-based educational activity, participants should be able to

- Outline elements of a systems approach to managing reversal of oral anticoagulant therapy.
- Apply practical considerations in the dosing and timing of agents used to reverse oral anticoagulant therapy.

CONTINUING EDUCATION ACCREDITATION

The American Society of Health-System Pharmacists is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. This activity provides 1.0 hour (0.1 CEU) of continuing pharmacy education credit (ACPE activity #0204-0000-13-400-L01-P).

Attendees must complete a Continuing Pharmacy Education Request online and may immediately print their official statements of continuing pharmacy education (CPE) credit following the activity.

Complete instructions for processing CE can be found on the last page of this handout.

Additional Educational Opportunities on this Topic

- On-demand activity entitled, “Emerging Treatment Options for the Reversal of Oral Anticoagulant Therapy” (2 hours CPE)
- Informational recordings featuring the faculty in a roundtable discussion about important issues related to reversal of oral anticoagulant therapy
- e-Newsletters featuring updates on emerging information, as well as tips for incorporating information related to the reversal of oral anticoagulant therapy into practice (coming soon)

www.ashpadvantage.com/reversal
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Learning Objectives
At the conclusion of this presentation, participants will be able to
• Outline elements of a systems approach to managing reversal of oral anticoagulant therapy
• Apply practical considerations in the dosing and timing of agents used to reverse oral anticoagulant therapy

Clinical Challenges in Reversal of Oral Anticoagulants

Warfarin
• Vitamin K
• Concentrated blood factors > FFP alone
  – All studies have some methodologic limitations

Novel oral anticoagulants
• Lack of antidote
• Concentrated blood factors may have a role
  – aPCC or 4-factor PCCs may be best approach
  – Extremely limited data, human data lacking
• Large gaps in knowledge about best approach
• Proper patient selection is critical

Patient Scenario: LC
LC, a 75-year-old woman, presents with new onset loss of consciousness and is found to have ICH.
• Takes rivaroxaban 20 mg daily for AF
  – CHADS2 score = 6
• INR is 7.2 today

Which of the following could be used to reverse the anticoagulant effect of rivaroxaban in this patient?

- An activated PCC
- A 3-factor PCC
- A 4-factor PCC
- A 3-factor PCC plus rFVIIa
- rFVIIa

rFVIIa = recombinant factor VIIa

Importance of a Systems Approach
• Implementation of a coordinated approach
  – Agent selection for formulary & product stocking
  – Access to reversal agents & other interventions
  – Rapid ability to implement management options
    • 24-hour process; avoid delays in treatment
• Clinical and operational guidelines
  – Risk assessment (thrombosis, bleeding, acuity)
  – How to select, dose, monitor available agents
  – Correct laboratory tests available
  – Centralized, easy for clinicians to locate, flexible
    • Role of health informatics and clinical decision support
Key Stakeholders and Multidisciplinary Input
- Emergency and trauma physicians
- Hematologists, nephrologists
- Pharmacists, nurses
- Intensivists, including neuro-intensivists
- Neurosurgeons and other surgeons
- Clinical laboratory personnel
- Blood bank representatives
- Risk managers
- Health informatics professionals

Risk Assessment
- Patients should be stratified based on the urgency of the need for intervention
  - Patients for whom no action is needed within 24 hours (i.e., no rush to make a decision)
  - Patients for whom an expedited decision is needed within 1-24 hours
  - Patients with an emergent need for intervention within 1 hour (e.g., patients with life-threatening bleeding or an urgent need for a procedure or operation)

Reversal of Warfarin: Agent Selection
- Options
  - IV vitamin K
  - Fresh frozen plasma
  - Prothrombin complex concentrate
  - Recombinant factor VIIa (rFVIIa)
  - Activated PCC

Reversal of Warfarin: Agent Selection

<table>
<thead>
<tr>
<th>Clinical Scenario</th>
<th>Reversal Approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding</td>
<td>Vitamin K 5 – 10 mg slow i.v. + 4-factor PCC†</td>
</tr>
<tr>
<td>Surgery in &lt; 24 hours</td>
<td>Vitamin K 5 – 10 mg slow i.v. + Either 4-factor PCC†, rFVIIa or aPCC‡</td>
</tr>
<tr>
<td>Surgery in &gt; 24 hours</td>
<td>May have time to use i.v. vitamin K alone†</td>
</tr>
</tbody>
</table>

†Recommendation based on CHEST Guidelines (2C).
‡Recommendation based on published literature and pharmacodynamics of vitamin K.
*Note: 4-factor PCC not yet available in the United States; FFP or rFVIIa may be needed in addition to a 3-factor PCC to achieve desired effect on INR.

Reversal of New Oral Anticoagulants: Agent Selection
Possible strategies
- aPCC
  - Supported by animal and limited human data
- 3-factor PCC plus rFVIIa
  - Mimic effects of aPCC
- Maybe a 4-factor PCC
  - Conflicting animal data, limited human data

References:
Reversal of New Oral Anticoagulants: Practical Considerations

**Dabigatran**
- Charcoal after recent ingestion
- Renal impairment complicates reversal
  - Role for hemodialysis

**Rivaroxaban and apixaban**
- Less reliance on renal clearance

**Dosing**
- Very little guidance
  - Higher doses than usual?

**Patient selection**
- Risk vs. benefit

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**Concentrated Blood Factor Products**

<table>
<thead>
<tr>
<th>Brand Names</th>
<th>rFVIIa</th>
<th>3-Factor PCC</th>
<th>4-Factor PCC</th>
<th>aPCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>NovoSeven®</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Bebulin VHP®</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Profilnine SD®</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Octaplex®</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beriplex P/N®</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cofact®</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kanokad®</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>U.S. Availability</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Factors Provided</td>
<td>VII</td>
<td>II, IX, X</td>
<td>II, VII, IX, X</td>
<td>II, VII, IX, X</td>
</tr>
<tr>
<td>Activated?</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>


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**What can we do in the United States?**

- Add FFP to either 3-factor PCC or rFVIIa
  - FFP may not be tolerated by all
- 3-factor PCC + rFVIIa
- aPCC alone

4-factor PCC approval soon?

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**Formulary Agent Selection and Cost Implications**

<table>
<thead>
<tr>
<th>Agent</th>
<th>FFP + PCC</th>
<th>PCC + rFVIIa</th>
<th>aPCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFP (15 mL/kg)</td>
<td>$300</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-factor PCC (25 units/kg)</td>
<td>$1932</td>
<td>$1932</td>
<td></td>
</tr>
<tr>
<td>rFVIIa (20 mcg/kg)</td>
<td></td>
<td>$2820</td>
<td></td>
</tr>
<tr>
<td>aPCC (1000 units)</td>
<td></td>
<td></td>
<td>$1800</td>
</tr>
<tr>
<td>Cost/reversal regimen</td>
<td>$2232</td>
<td>$4752</td>
<td>$1800</td>
</tr>
</tbody>
</table>

*Assumes 80-kg patient and rounding to nearest vial size.
Acquisition cost (average wholesale price) for FFP = $60 per unit, PCC = $0.97/unit, rFVIIa = $1410/1-mg vial, aPCC = $1800/1056 units

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**“Building” a 4-Factor PCC**

**Patients**
- Warfarin related ICH, INR ≥ 1.6 (46)
- Historical controls (12)

**Reversal strategy**
- Vitamin K 5 mg slow i.v.
- PCC 4000 units
- rFVIIa 1 mg

**Complications**
- 2 NSTEMI
  - 1 occurred 8 hours post PCC + rFVIIa
  - 1 occurred 3 days later
- Mortality
  - 24 hours – 5/46
  - 72 hours – 8/46

*PCC+rFVIIa less than FFP and PCC+FFP (p<0.05)*


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**Reversing Warfarin**

**Vitamin K (i.v. or oral): 0.25–10 mg**

**FFP**

**PCC**
- 3-factor PCC vs. 4-factor PCC vs. aPCC
- 25-50 units/kg depending on patient’s weight, INR, and bleeding

**Recombinant activated factor VII**
- Low dose (1-2 mg) vs. high dose


A patient on warfarin is admitted with INR of 6 and blood in stools. What would you consider false about use of vitamin K here?

- a. S.C. vitamin K drops the INR faster than oral vitamin K
- b. INR at 24 hr is similar after i.v. or oral vitamin K
- c. Repeat INR may be advisable
- d. Effects of vitamin K are gone within days

**Vitamin K to Reverse Warfarin**

Vitamin K (i.v. or oral): (0.25–10 mg)
- Initial INR
- Target INR after vitamin K
- Plans for re-anticoagulation
  - 10-40 mg i.v.: Effects can last days to weeks
- Intravenous: INR starts dropping in 4-12 hr
  - 0.25-1 mg will decrease a INR > 6 to <3.0
  - IV form can be administered PO
  - Anaphylaxis: Incidence is ~1:3500
    - Infuse over ~ 15 minutes

**Vitamin K for Reversal of Warfarin**

- Intravenous vitamin K included in studies of other management strategies

**Vitamin K: Oral vs. Subcutaneous (SC)**

<table>
<thead>
<tr>
<th>Mean INR</th>
<th>1 mg Oral*</th>
<th>1 mg SC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial (range 4.5-10)</td>
<td>5.6</td>
<td>6.2</td>
</tr>
<tr>
<td>Day 1</td>
<td>2.9</td>
<td>4.2</td>
</tr>
<tr>
<td>Day 2</td>
<td>2.2</td>
<td>3.1</td>
</tr>
<tr>
<td>Day 3</td>
<td>2.7</td>
<td>2.8</td>
</tr>
</tbody>
</table>

SC: unpredictable and smaller initial drop in the INR compared with oral administration

**Prothrombin Complex Concentrates**

- 25-50 units/kg
  - Dosing weight: ideal vs. actual, or nearest vial size
  - Rapid administration and onset of effect
  - Higher dose if INR higher
  - Expensive
  - Variable products
    - 3 or 4 factors: II,IX,X (+/- VII)
    - aPCC

**References**


What Improves Outcomes in Warfarin-related ICH?

- A good stitch – STICH Trial: ? Any impact of neurosurgery on improved outcomes
- Dowlatshahi et al. Stroke. 2012
- PCC rapidly reversed the INR, but did not change mortality and morbidity
- PCC shorten time to surgical procedures – Surgery may improve ICU-related outcomes
- Caution rebound – Effects rapid
- Retrospective studies may not have controlled for post-PCC INR measurement times


rFVIIa to Reverse Warfarin Effects

<table>
<thead>
<tr>
<th>Year</th>
<th>n</th>
<th>Dose</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003</td>
<td>7</td>
<td>10-40 mcg/kg</td>
<td>INR1.5 at 10 min and adequate hemostasis at surgery</td>
</tr>
<tr>
<td>2003</td>
<td>4</td>
<td>1200 mcg</td>
<td>Normal INR in 2 hours</td>
</tr>
<tr>
<td>2004</td>
<td>7</td>
<td>15-90 mcg/kg</td>
<td>Rapid correction of INR</td>
</tr>
<tr>
<td>2005</td>
<td>12</td>
<td>2400-9600 mcg</td>
<td>Rapid correction with less FFP; outcome unchanged</td>
</tr>
<tr>
<td>2005</td>
<td>29</td>
<td>1200-2400 mcg</td>
<td>Faster correction of INR and improved outcome</td>
</tr>
<tr>
<td>2006</td>
<td>30</td>
<td>10-100 mcg/kg</td>
<td>Faster correction with less FFP</td>
</tr>
<tr>
<td>2008</td>
<td>16</td>
<td>1200 mcg</td>
<td>Mean INR ↓ 2.8 – 1.07 within mean of 35 min. Rapid and favorable response in INR and hemostatic affect in 14 of 16 patients</td>
</tr>
<tr>
<td>2010</td>
<td>20/20</td>
<td>1200 mcg</td>
<td>ICH rFVIIa tx vs. not, 20 patients each, matched - No difference in thromboembolic events or survival</td>
</tr>
</tbody>
</table>


Reversing Warfarin

A patient on warfarin requires emergent reversal of the INR to 1.0. Which of the following is true?

a. Use PCC3 25 units – contains high amounts of factor VII
b. Use PCC3 50 units/kg – effect lasts longer than warfarin
c. Use PCC4 25 units/kg – commonly available in U.S.
d. Use PCC3 or PCC4 – will drop the INR in minutes

PCC3 = 3-factor PCC
PCC4 = 4-factor PCC

Antifibrinolytic Agents

- Aminocaproic acid
  - 80-150 mg/kg (5-10 g) then 2.5–30 mg/kg/hr (1-2.5 g/hr)
- Tranexamic acid
  - Generally: 10-20 mg/kg (~2.5 g bolus) then 2-40 mg/kg/hr
  - Cardiothoracic (CT) surgery: 10 mg/kg bolus then 1 mg/kg/hr for 10-12 hours
  - Depending on the setting (orthopedic surgery < CT surgery < hepatic surgery)

Voils S. Pharmacotherapy. 2007; 27(9 pt 2):69S-84S.

Is There a Way to Reverse these Agents?

<table>
<thead>
<tr>
<th>ETP A endogenous thrombin potential</th>
<th>Dubigatran</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1/2 14-17 hr</td>
<td>80%</td>
<td>90%</td>
</tr>
<tr>
<td>Hemodialysis Yes ~2/3 in 2 hr</td>
<td>Not expected (&gt; 80% bound)</td>
<td>(Apixaban: 87% bound)</td>
</tr>
<tr>
<td>Antidote</td>
<td>In development</td>
<td>In development</td>
</tr>
<tr>
<td>Hemostatic Agents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-factor PCC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Did not restore aPTT, ECT, TT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- rFVIIa altered ETP lag time</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- PCC response on correcting ETP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; rFVIIa response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Activated PCC (aPCC)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Most notable correction ETP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Effective – single case (25 units/kg)</td>
<td>Corrected all parameters</td>
<td></td>
</tr>
<tr>
<td>- rFVIIa (high dose)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- CABG: Limited effect, high dose, single case</td>
<td>Corrected lag time</td>
<td></td>
</tr>
</tbody>
</table>

Assessing Intensity of Anticoagulation Effects

<table>
<thead>
<tr>
<th>Drug present</th>
<th>Thrombin time</th>
<th>Chromogenic anti-factor Xa</th>
<th>High sensitive INR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quantitative test</td>
<td>? Dilute thrombin time or Chromogenic ECT</td>
<td>Chromogenic anti-factor Xa</td>
<td></td>
</tr>
<tr>
<td>Sensitivity: PT vs. aPTT</td>
<td>aPTT &gt; PT (Point-of-care INR &gt; central lab)</td>
<td>PT &gt; aPTT</td>
<td></td>
</tr>
<tr>
<td>No or limited effect</td>
<td>ECT, TT</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Normal INR or aPTT values can occur at trough or active levels

What does a value mean?
- Is there a safe level to operate?
- Is it too high where the dose should be lowered?

Lindhoff-Last E et al. Ther Drug Monit. 2010; 32:673-9;

Effects of Dabigatran on PT, aPTT, and TT


Restarting Anticoagulation

- Assessment of thrombosis vs. bleeding
  - Continuous assessment
- Warfarin
  - Witt et al. S/P GI bleed: n = 442
    - Resuming warfarin associated with decrease in thrombosis and death
    - No significant increase in recurrent GI bleed
- Dabigatan
- Rivaroxaban and apixaban


Patient Scenario: LC

LC, a 75-year-old woman, presents with new onset loss of consciousness and is found to have ICH. She takes rivaroxaban 20 mg daily for AF (CHADS2 score = 6), INR = 7.2 on admit.

Anticoagulation was reversed with FFP and aPCC. The patient was stabilized.

Should LC resume rivaroxaban or another anticoagulant agent?
- a. Yes
- b. No
- c. I’m not sure

How long is it safe to withhold rivaroxaban in this patient?
- a. Indefinitely
- b. 7 days
- c. 14 days
- d. 30 days
- e. Use alternate anticoagulant once patient is stabilized
Transition of Care Issues

- Long-term challenges in patients whose oral anticoagulant therapy has been reversed
- Whether to re-anticoagulate
- When to restart
- What agent
- What dose
- Long-term monitoring plan

Transition of Care Issues

- Policies and procedures established to avoid delays in obtaining reversal therapies
  - May need to transfer patient to another institution where necessary therapy is available
  - Develop plan that addresses transportation and communication about patient status
    - Time since last oral anticoagulant dose
    - Use of activated charcoal and reversal agents
  - Establish patient transfer agreements before an emergent need arises
  - Communicate reversal plan with local emergency medical services personnel
Effects of Dabigatran on PT, aPTT, and TT

SELECTED REFERENCES


Ask the Experts: Developing a Systems Approach for Managing Reversal of Oral Anticoagulant Therapy


**SELF-ASSESSMENT QUESTIONS**

1. A systems approach for managing reversal of oral anticoagulant therapy should be implemented that ensures the ability to implement management options
   
   a. Within 12 hours of patient admission.
   b. Within 24 hours of patient admission.
   c. Around the clock to avoid any delays in treatment.
   d. Upon approval of a pharmacist who is responsible for reviewing orders for all factor products.

2. A 56-year-old woman taking warfarin is admitted with INR of 6 and blood in stools. All of the following considerations about the use of vitamin K in this patient is true EXCEPT
   
   a. Vitamin K administered subcutaneously drops the INR faster than oral vitamin K.
   b. INR at 24 hours is similar after i.v. or oral vitamin K.
   c. Effects of vitamin K are gone within days.
   d. It may be advisable to repeat the INR.

3. A patient on warfarin requires emergent reversal of the INR to 1.0. Which of the following statements about treatment options is true?
   
   a. Use a 3-factor prothrombin complex concentrate (PCC) 25 units – contains high amounts of factor VII.
   b. Use a 3-factor PCC 50 units/kg – effect lasts longer than warfarin.
   c. Use a 4-factor PCC 25 units/kg – commonly available in U.S.
   d. Use a 3-factor or 4-factor PCC – will drop the INR in minutes.

4. PV is a 72-year-old man who was admitted with new-onset loss of consciousness and was found to have an intracranial hemorrhage. He was taking rivaroxaban 20 mg daily for atrial fibrillation (CHADS2 score = 6). On admission, his INR was 7.2. Rivaroxaban was discontinued, and anticoagulation was reversed with fresh frozen plasma and activated PCC. The patient was stabilized. Should PV resume rivaroxaban or another anticoagulant agent?
   
   a. Yes.
   b. No.

5. How long is it safe to withhold rivaroxaban in this patient?
   
   a. 7 days.
   b. 14 days.
   c. 30 days.
   d. Indefinitely.
   e. Use alternate anticoagulant once patient is stabilized.

**Answers**

1. c  2. c  3. d  4. a  5. e
Ask the Experts: Developing a Systems Approach for Managing Reversal of Oral Anticoagulant Therapy

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