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TITLE: Principles of Oral Anticoagulant Reversal
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Slide 1:
Hello, my name is Minh-Ha Tran. I am a Transfusion Medicine physician at the University of California, Irvine Medical Center. Welcome to this Pearl of Laboratory Medicine on Principles of Oral Anticoagulant Reversal.

Slide 2:
After participating in this activity, learners will be able to 1) Describe general pharmacologic properties of modern oral anticoagulants, 2) Understand aspects of principal reversal strategies, and 3) Develop a therapeutic approach toward anticoagulant related bleeding.

Slide 3:
A simplified representation of the coagulation cascade is presented here. Detailed elaboration upon coagulation science and related testing is beyond the scope of this presentation. The vitamin K dependent procoagulant factors – II, VII, IX, and X – are in red.

Oral anticoagulant therapy limits the thrombotic potential of blood either indirectly through interference with coagulation factor production or directly through inhibition of specific factors. Warfarin – a vitamin K antagonist – interferes with the final gamma-carboxylation step required for vitamin K dependent factors to become fully functional. Warfarin is characterized by a long duration of effect with a half-life of over 30 hours. Renal impairment does not affect its metabolism but there are numerous drug-drug interactions which can either potentiate or reduce its effect.

Upon initiation of warfarin, the typical circumstance is to first observe prolongation of PT/INR owing to reduction in Factor VII, which has the shortest circulating half-life. As the longer-lived factors begin to decline, the PTT becomes prolonged as well. PT/PTT Mixing studies would generally be expected to correct in the setting warfarin effect.

The Non-vitamin K Oral Anti-Coagulants (NOACs) – induce anticoagulation through direct inhibition of specific targets. In general, they can be distinguished from Warfarin by their rapid onset of anticoagulant effect, short duration of activity (half-lives around 15 hours or less), and

fewer drug-drug interactions. In contrast to warfarin, renal impairment can lead prolonged NOAC effect – particularly in the case of Dabigatran.

The Factor Xa Inhibitors, have a more prominent effect upon the PT but both PT and PTT may be prolonged to a variable degree. PT/PTT mixing studies demonstrate the presence of an inhibitor. The anti-FXa activity level is a useful test to determine residual Factor Xa inhibitor effect.

The Direct Thrombin Inhibitor, Dabigatran has a more prominent effect upon the PTT but both PT and PTT may be prolonged to a variable degree. PT/PTT mixing studies demonstrate the presence of an inhibitor. The Thrombin Time is a useful, albeit qualitative, test to determine residual Dabigatran effect. Provided these tests are within normal limits (ie, undetectable Factor Xa effect or no prolongation of TT) then significant residual drug effect is unexpected.

Slide 4:
Reversal strategies in the first category are aimed at facilitating endogenous recovery of hemostatic potential. Discontinuation of the oral anticoagulant is the first step in allowing normalization of coagulation status. In the case of warfarin, this normalization process is hastened by administration of vitamin K.

For Vitamin K PO doses generally range between 5-10 mg whereas IV doses between 1-5 mg. Anaphylactoid reactions to IV Vitamin K and to plasma are very rare, and risk is likely to be similar between these two options.

Reversal strategies in the second category represent administration of exogenous coagulation factors. Plasma is a source of all procoagulant and anticoagulant factors, but is associated with preparation time, volume challenge (dosed at 15-20 mL/kg), risk of transfusion reactions, and imparts only a limited duration of impact upon the INR. Prothrombin Complex Concentrates (PCC) are comprised mainly of vitamin K dependent factors and can be reconstituted to a very low-volume administration dose. KCENTRA (CSL Behring GmbH, Marburg, Germany) is a 4-factor PCC approved in the US for reversal of warfarin effect in selected patients. Dosing, which is guided by degree of INR elevation, ranges from 25-50 FIX U/kg (not to exceed 100 kg in dose calculation).

Plasma and PCC bear thrombogenic potential and may therefore induce clot formation. Plasma is unlikely to have any benefit in terms of NOAC reversal. Although PCC have been suggested as a NOAC reversal agent, data are lacking in terms of safety and efficacy for this off-label use.

Reversal strategies in the third category involve targeted antidotes – the two covered in this review specifically bind and neutralize NOACs. Idarucizumab (Boerhinger Ingelheim

Pharmaceuticals, Ridgefield, CT) is a monoclonal antibody that binds with higher affinity to dabigatran (and its metabolites) than thrombin, thus neutralizing its dabigatran effect. Andexanet alfa (Portola Pharmaceuticals, San Francisco, CA) is a Factor Xa 'decoy molecule' that outcompetes endogenous Factor Xa for the Factor Xa inhibitors. As of the time of writing, Andexanet is not yet approved.

These two agents are not associated with known thrombogenic potential, but reversal of anticoagulation now returns the patient to their original thrombotic risk status, which may be additionally heightened by acute medical illness.

Slide 5:
It is important to assess for concomitant coagulopathy, which may be suggested when coagulation parameters fail to normalize as expected. If present, such competing etiologies for coagulopathy may require additional treatment considerations.

In regards to plasma/PCC, the greatest potential impact upon INR is expected when the INR is 2 or greater. In circumstances where the baseline INR is less than 2, the INR reduction – particularly from plasma – is negligible.

As noted in the prior slide, administration of exogenous clotting factors bears thrombogenic implications. Careful judgement must therefore be exercised prior to administration of these agents when bleeding is not life-threatening.

Slide 6:
Anticoagulant reversal and especially hemostatic agent therapy are associated with heightened thrombotic risk. Because of this, the patient's underlying risk for thrombosis should be taken into account. This table discusses scenarios where thrombotic risk may be especially high. In such scenarios, administration of aggressive hemostatic therapy should likely be avoided unless strong clinical justification exists (ie, intracranial hemorrhage).

Slide 7:
This graph illustrates the expected dissipation of warfarin effect following cessation. The X axis is divided into successive half-lives since last administration. The Y axis represents warfarin effect. If a patient is not bleeding, but the INR is supratherapeutic, it is acceptable simply to hold the next dose or two of warfarin and resume at a lower dose once the INR has re-entered the desired therapeutic range.

If bleeding is present but isn't life-threatening, then administration of vitamin K results in more rapid reversal of warfarin effect. In one study, authors found that 1-5 mg IV resulted in some reduction in INR by 6 hours and majority of reversal effect was in place by 15 hours.

In many cases, bleeding can be safely managed simply by holding warfarin and administering vitamin K. Hemodynamic support with intravenous fluids and blood transfusions will aid in stabilizing the patient. If bleeding is localized to a specific bleeding site – compression or other appropriate local measures – are indicated.

In some circumstances, sequelae of bleeding may be so severe that even the short time required for vitamin K effect to become established – represented by the yellow bracket – becomes unacceptable. In such circumstances, administration of donor-derived clotting factors – either as plasma or as prothrombin complex concentrate – becomes indicated, allowing for a more immediate reversal effect.

Administration of exogenous clotting factors or hemostatic agents (ie, plasma, PCC, recombinant human factor VIIa) is associated with the risk of inducing iatrogenic thrombosis. This concern is especially valid in patients with the high-thrombotic risk features described in the previous slide. Such patients should – in most cases – be re-anticoagulated expeditiously once the bleeding event has been addressed owing to high underlying thrombotic risk.

Slide 8:

Identifying the specific agent, time of last dose, recent changes to the medication regimen, and presence of renal impairment are key toward approaching NOAC-related bleeding.

If the patient is on a Factor Xa inhibitor, and the last dose was over 24 hours ago, then approximately two half-lives have now passed and little residual effect is expected. If coagulation status fails to normalize as time passes, then an alternative etiology (e.g., DIC, underlying factor deficiency, etc) is likely present. Factor Xa inhibitors are less sensitive to renal impairment than dabigatran.

If renal function is preserved, and bleeding non-severe, then simply holding the NOAC may be all that is necessary. Difficulty is encountered if the time since last dose is relatively recent (within 1 half-life of the agent) or cannot be established.

For the Factor Xa inhibitors, the anti-Factor Xa activity level (similar to a heparin level, ideally using drug-specific calibrators) can be useful in assessing for the presence of residual anticoagulant effect. In the setting of dabigatran, the Thrombin Time (or a purpose-driven dilute Thrombin Time) serves the same purpose. Prolongation of either suggests that drug effect persists.

If administration was very recent – within a few hours – activated charcoal may be administered to prevent further absorption. Dabigatran effect can now be immediately reversed with Idarucizumab if severe bleeding or an indication for urgent/emergent surgery should arise.

The dabigatran-specific reversal agent Idarucizumab (Praxbind) is a monoclonal antibody now available that binds dabigatran and its metabolites with higher affinity than dabigatran for its target thrombin, thus neutralizing the dabigatran effect.

The equivalent antidote for Factor Xa inhibitors – Andexanet alfa – is not yet approved at time of writing. Clinical trials are underway assessing its efficacy and optimal dosing.

Although PCC has been advised as an option to address severe NOAC-related bleeding, there is little in the way of clinical data to support its efficacy in restoring hemostatic competence. If this agent is under consideration, then the same discussion of thrombotic risk applies.

Slides 9-10:

In conclusion, when faced with a bleeding patient information gathering is critical. Ascertain the specific anticoagulant and time of last dose. Determine the site and severity of bleeding and inquire whether emergent surgery is indicated as a consequence. Life threatening bleeding or emergent surgery need elevates the urgency for reversal.

Inquire about drug-drug interactions – asking whether any new medications have been recently prescribed or added to the regimen is useful. Depending upon the patient's clinical status, it may become necessary to obtain information from alternate sources – such as the patient's pharmacy, physician, or family members.

Assess for comorbidities that heighten thrombotic risk. Such factors will impact decision-making when selecting a reversal strategy, particularly when sequelae of bleeding appear manageable with less aggressive maneuvers.

Slide 10:

In the setting of warfarin anticoagulation, the INR is a critical piece of information. For minor elevations, plasma is unlikely to produce a meaningful INR response. Durable reversal requires administration of vitamin K. The intravenous route is preferred during urgent reversals and the risk of anaphylactoid reactions is low. IV vitamin K may require up to 6-15 hours to establish an effect, in the meantime, life-threatening bleeding or requirement for emergent surgery may necessitate administration of PCC or plasma. The latter has a particularly short duration of impact upon the INR, and re-prolongation may occur.

The NOACs are characterized by a short duration of effect. For non-life threatening bleeding, and particularly if renal function is preserved, supportive therapy, careful observation, and tincture of time may suffice. For Dabigatran, a targeted antidote – idarucizumab – is now

available for life-threatening bleeds or reversal of effect if the need for emergent surgery arises. For the Factor Xa inhibitors, a targeted antidote – Andexanet alfa – is currently undergoing clinical trials, but PCC has been promoted in the setting of life-threatening bleeding. Data are lacking, however, for this option so local protocols/guidelines should be consulted.

Slide 10: References
Slide 11: Additional Pharmacologic information
Slide 12: Disclosures

Slide 13: Thank You from www.TraineeCouncil.org
Thank you for joining me on this Pearl of Laboratory Medicine on "**Principles of Oral Anticoagulant Reversal**."