PALLIATIVE PEARLS
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Oral Anticoagulant Conversion Considerations
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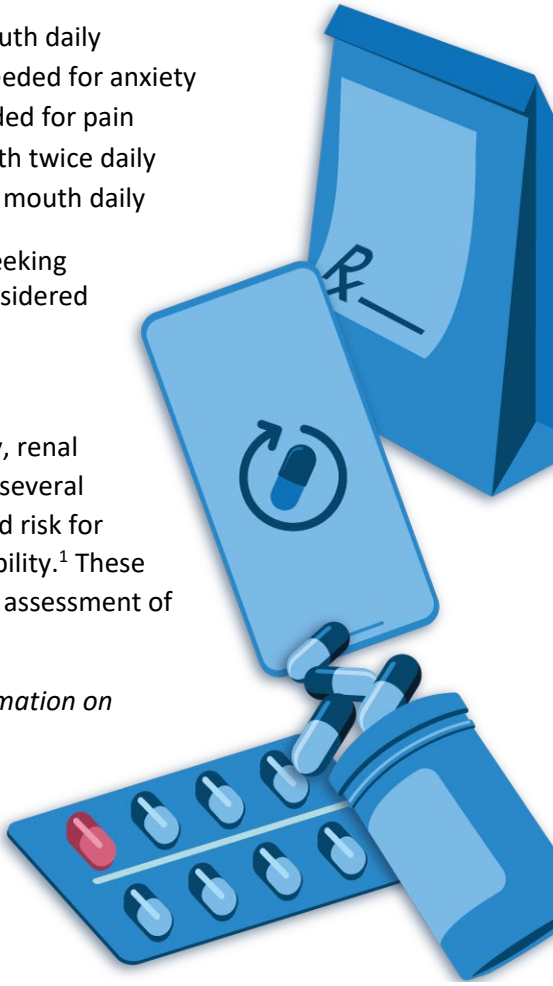
PATIENT CASE

JS is a 75-year-old male with a primary diagnosis of Hodgkin's lymphoma with a history of atrial fibrillation and stage 2 chronic kidney disease. He has no known drug allergies and is receiving hospice care at home.

MEDICATIONS

- Apixaban (Eliquis®) 2.5mg; 1 tablet by mouth twice daily
- Carvedilol (Coreg®) 12.5mg; 1 tablet by mouth twice daily
- Diltiazem extended-release (Cardizem® LA) 180mg; 1 tablet by mouth daily
- Lorazepam (Ativan®) 0.5mg; 1 tablet by mouth every 6 hours as needed for anxiety
- Oxycodone (OxyIR®) 5mg; 1 tablet by mouth every 4 hours as needed for pain
- Oxycodone extended-release (OxyContin®) 20mg; 1 tablet by mouth twice daily
- Polyethylene glycol (Miralax®) 17 grams dissolved in 8 oz water by mouth daily



Apixaban is a non-formulary medication for this hospice and the team is seeking guidance on a cost-effective alternative medication. What needs to be considered before making a recommendation?

ANTICOAGULATION IN THE HOSPICE POPULATION

In addition to acquired risk factors, such as disease states (e.g., malignancy, renal disease, liver disease, heart failure) and prescribed medications, there are several factors that place patients receiving hospice and palliative care at increased risk for venous thromboembolism. These include advanced aged and reduced mobility.[1] These same patients are also at risk for bleeding events necessitating a continual assessment of anticoagulation benefit and choice of therapy.[2,3]

See Palliative Pearls case Oral Anticoagulant Use in Hospice for more information on anticoagulation risks.

Patients with a history of atrial fibrillation, like JS, have a high risk of ischemic stroke and other embolic events. For many, anticoagulation therapy to prevent a thrombotic event outweighs the increased risk of bleeding. Over the last decade, options for anticoagulation therapy have expanded, providing clinicians more options.[4]

Joining unfractionated heparin (UFH), low molecular weight heparin (LMWH) (e.g., enoxaparin) and vitamin K antagonists (VKA) (e.g., warfarin), are the direct oral anticoagulants (DOACs). These novel oral agents do not require laboratory testing, administration is not painful like heparin and LMWH, and they lack limitations placed on diet and patient lifestyle (e.g., tobacco and alcohol use) by warfarin. However, the advantages of DOACs must be weighed with their cost-prohibitiveness.[5-7]

AGENTS AND CONSIDERATIONS

VKA

Several clotting factors (II, VII, IX) are dependent on vitamin K in the clotting cascade. In the outpatient setting, many may select VKA due to its inexpensiveness and clinician experience with dosing. Warfarin (Coumadin®, Jantoven®), the sole product in this class, has a narrow therapeutic window. It takes approximately 3 days to reach a therapeutic level when initiating therapy, requiring bridge therapy with a quicker onset anticoagulant (e.g., heparin) simultaneously until that level is achieved. Warfarin requires routine lab monitoring (INR) to ensure therapy remains in a therapeutic range and monitoring for signs of bleeding.

Inconsistent diet, lifestyle (e.g., tobacco use, alcohol consumption), and adherence can have drastic effects on a patient's INR level.[8] Warfarin dosing does not require adjustment for renal impairment and is metabolized in the liver via the cytochrome P450 (CYP450) enzyme system.[6] The CYP450 system consists of several isoenzymes (1A2, 2C8, 2C9, 2C19, 2D6, 3A4) designated for medication metabolism. Medications, like warfarin, affected by one or more of these enzymes are called substrates. Medications that slow metabolism of substrates are called inhibitors and those that speed up metabolism are called inducers.

The Indiana University School of Medicine maintains an interactive CYP450 drug interaction table that may be perused for review or searched for specific medications.[9,10] See Palliative Pearls case Drug Interactions in Hospice: Important Considerations for more information on CYP450 drug interactions.

Direct Oral Anticoagulants (DOACs)

Direct Thrombin Inhibitors – Fibrin is an insoluble protein that impedes the flow of blood. Thrombin is the enzyme that converts fibrinogen into fibrin in the final step in the clotting cascade. Dabigatran (Pradaxa®) is the only oral agent in this class.

Oral Factor Xa Inhibitors – These agents act immediately upstream of thrombin in the clotting cascade. Inhibiting Factor Xa prevents the conversion of prothrombin into thrombin.[11]

- Apixaban (Eliquis®)
- Rivaroxaban (Xarelto®)
- Edoxaban (Savaysa®)
- Betrixaban (Bevyxxa®)

DOACs do not require routine lab monitoring and exert their therapeutic effect within hours.[6,12] Despite their advantages over UFH, LMWH and VKA, they still require monitoring for signs of bleeding.

Dose adjustment of DOACs in mild to moderate renal disease (CrCl 30 to 50ml/min) and safety and efficacy of use in severe renal disease (CrCl < 30ml/min) is often dependent on the agent and indication for anticoagulation (e.g., stroke prevention).[5] It is prudent to weigh the benefits and risks of DOACs with patient disease states to determine the appropriateness of specific DOACs in renal disease population.

Individual DOACs are substrates for p-glycoprotein (P-gp) and/or CYP450. P-gp is a drug efflux pump found in the gut, liver, kidney, blood-brain barrier, and cancer cells that pumps drugs out of cells and into the gut, bile, and/or urine for excretion.[13] Strong P-gp inducers and/or inhibitors used with a DOAC may exacerbate the patient's risk for bleeding or reduce anticoagulation effectiveness.[6-8,14-18]

The U.S. Food & Drug Administration maintains a resource with information on both CYP450 and P-gb drug interactions. Access Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers for more information.[8,19]

TRANSITIONING BETWEEN ORAL AGENTS

Recognize that this juncture is also an opportunity to weigh the risks and benefits of anticoagulation overall and begin deprescribing conversations with the patient and caregivers. This may not be the right time to stop anticoagulation however the risks of therapy will eventually outweigh the benefits as end of life nears and it's important to prepare for this inevitability.

When transitioning between anticoagulants, the goal is to maintain stable anticoagulation. Newer agents have more predictable therapeutic responses and less impact on a patient's lifestyle.[5] In most instances, transitioning to warfarin is chosen to mitigate costs. Consideration of kidney function, concomitant medications, lifestyle, and goals of care are recommended.

Switching FROM a direct oral anticoagulant TO warfarin:

Dabigatran TO warfarin[14]

- The two agents are to be overlapped. The number of days of overlap depends on the patient's renal function:
    - Creatinine clearance (CrCl) ≥50 mL/minute – start warfarin 3 days before discontinuing dabigatran
    - CrCl 30 to 50 mL/minute – start warfarin 2 days before discontinuing dabigatran
    - CrCl 15 to 30 mL/minute – start warfarin 1 day before discontinuing dabigatran
    - CrCl < 15 mL/min – no recommendation can be made

Apixaban TO warfarin[15]

- Stop apixaban and start parenteral anticoagulant during warfarin initiation. Warfarin INR should be within therapeutic INR range for 2 to 3 days for full anticoagulation to occur.

Rivaroxaban TO warfarin[7]

- Stop rivaroxaban and start parenteral anticoagulant during warfarin initiation. Warfarin INR should be within therapeutic INR range for 2 to 3 days for full anticoagulation to occur.

Edoxaban TO warfarin[16]

- Patients on 60mg of edoxaban – reduce dose to 30mg and begin warfarin concomitantly
- Patients on 30mg of edoxaban – reduce dose to 15mg and begin warfarin concomitantly

Bextrixaban TO warfarin[5]

- No transition has been recommended as bextrixaban is only used for VTE Prophylaxis

The American Society of Hematology (ASH) suggests an alternative approach of overlapping warfarin with previous therapy of factor Xa inhibitors until INR is therapeutic. Factor Xa inhibitors prolong the PT/INR time, therefore the ASH guidelines recommend testing directly before the next dose of the factor Xa inhibitor to obtain the most accurate result.[17]

Switching FROM warfarin TO direct oral anticoagulant:[7,14-16]

- Warfarin TO dabigatran – Discontinue warfarin, and start dabigatran when the INR is < 2.0
- Warfarin TO apixaban - Discontinue warfarin, and start apixaban when the INR is < 2.0
- Warfarin TO rivaroxaban - Discontinue warfarin, and start rivaroxaban when the INR is < 3.0
- Warfarin TO edoxaban - Discontinue warfarin, and start edoxaban when the PT/INR is < 2.5

PATIENT ASSESSMENT & RECOMMENDATION

The hospice team discusses anticoagulant options with JS and his family. They come to a shared decision to transition JS from apixaban to the hospice formulary alternative, warfarin. Currently, JS has a consistent diet and has support at home for transport to a lab for regular INR testing. Based on lab results from a recent hospital discharge, JS is estimated to have a CrCl of 65ml/min.

Recognizing that warfarin takes presumably 3 days to reach therapeutic levels, the pharmacist recommends the overlap approach suggested by ASH[17] and recommends warfarin 5mg by mouth daily concomitantly with the apixaban. After day 3, and directly before the next apixaban dose is due, the lab draw for INR is recommended to confirm a therapeutic level. The pharmacist encourages the hospice to continue to monitor and adjust dosing accordingly to achieve the target INR – once reached, the apixaban may be discontinued.

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