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Navigating the Intersection of Antithrombotic Therapy & GI Bleeding

Dr. Buch:
Antithrombotic therapy including anticoagulants and antiplatelet therapy is the cornerstone for a variety of conditions. It is estimated that six million patients in the United States are treated with anticoagulants and many more are on antiplatelet therapy. The intersection of anticoagulants and GI issues can be problematic.

This is Dr. Peter Buch, your host for ReachMD *GI Insights*. Here to sort this all out is Adam Olsen. Mr. Olsen is the Department Chair and Program Director for the Master of Physician Assistant Studies Program at Sacred Heart University in Stamford, Connecticut. He is also a practicing cardiology PA and works for Northeast Medical Group Heart and Vascular Center.

Welcome to the program, Professor Olsen!

Mr. Olsen:
Thank you very much, Dr. Buch. That's a wonderful introduction. It's a pleasure to be with you today.

Dr. Buch:
Let's dive right in. When should we use fresh frozen plasma in patients with lower GI bleeding who are also taking warfarin?

Mr. Olsen:
Yeah, sure. So, administration of fresh frozen plasma, also known as FFP, for the reversal of warfarin as indicated for major GI bleeding or for life-threatening bleeding. So in the case of lower GI bleeding, we want to go ahead and define, well what is major bleeding or life-threatening bleeding, and that we can define as the presence of hemodynamic instability. So that's a blood pressure of less than 90 mmHg or mean arterial pressure less than 65 mmHg and also whether or not there is a drop in hemoglobin of greater than or equal to 2 grams. So warfarin as we know is a vitamin K antagonist. So certainly the first step in patients presenting with major lower GI bleeding is to stop the warfarin and to also administer IV vitamin K. Additionally, current guidelines outline that 4-factor prothrombin complex concentrate, also known as 4F PCC, is considered more of a first-line therapy when available, and the advantage of utilizing this therapy is that it provides more of a rapid reversal and it does not require ABO blood group compatibility. But when 4F PCC is not available, fresh frozen plasma should be administered, as FFP contains vitamin K clotting factors and other coagulation factors. One thing you need to think about with regards to FFP is the administration of FFP does require ABO blood group compatibility and will require several units. So one needs to be more cautious in your volume-sensitive patients, as 1 unit of plasma is approximately 300 mL.

Dr. Buch:
Let's now consider a major colonic bleed with Apixaban. What are the pros and cons of using Andexanet alfa?

Mr. Olsen:
Good question. So Apixaban, also known as Eliquis, is known as a direct oral anticoagulant and its mechanism of it action is it inhibits factor Xa. Andexanet alfa was the first reversal agent approved by the US Food and Drug Administration back in 2018 to treat life-threatening bleeding in patients on factor Xa inhibitors such as Apixaban or Rivaroxaban, which is known as Xarelto.

So the way Andexanet alfa works is it is a recombinant protein that binds to the anticoagulant to essentially inactivate it. In patients who are presenting with life-threatening bleeding when more conservative bleeding management measures have been ineffective, Andexanet has been shown to actually improve hemostasis 12 hours after infusion which is the major advantage to using this agent in this specific patient group. However, Andexanet has the potential to cause thrombosis which provides the rationale for only using it in cases of serious or life-threatening bleeding. It does carry a black-box warning regarding risks of arterial and venous thromboembolic and ischemic events, and one other thing to note about this is that it's actually very expensive. A 200-mg vial costs about $6,600 and

when you're giving this as a treatment for life-threatening bleeding typically several vials are needed, so it becomes a pretty expensive medication which is usually not in very large supply in hospital settings.

Dr. Buch:
Mr. Olsen, how do you decide how soon to reinitiate warfarin or Apixaban treatment after a GI bleed?

Mr. Olsen:
This is a great question and there is no one perfect answer. The timing of anticoagulant resumption needs to be individualized and based on the individual's underlying thromboembolic risk and the specific details of that bleeding event.

So the results from a very recent large retrospective study that was released in March of 2021 showed that restarting anticoagulation was associated with reduced thrombosis and reduced death. Not surprising though, there was a higher risk of re-bleeding. So generally the optimal time for restarting anticoagulation after a gastrointestinal bleed appears to be 7 to 14 days. It may be permanently deferred in selected patients with a very high risk of recurrent bleeding and in this unique population of patients, this is where you need to consider alternative therapies. For example, in a patient with atrial fibrillation who anticoagulation has been deemed to be completely contraindicated due to risk of recurrent bleeding, these patients may benefit from a left atrial closure device to reduce their risk of thromboembolic events.

Dr. Buch:
That's excellent. For those of you just joining us, this is Dr. Peter Buch for ReachMD. Joining me is Adam Olsen who is discussing anti-thrombotic therapy and GI bleeding.

Let's now turn to elective colonoscopies for patients on warfarin. Which patients need Enoxaparin bridge therapy?

Mr. Olsen:
Yeah. So, deciding whether or not to use bridge therapy is a common dilemma. When reviewing current guidelines, several factors need to be considered. Certainly determining the indication for the anticoagulation and whether that indication remains is one consideration, determining the patient's overall thromboembolic risk, and you know, we use scores like the CHADS VASc score in patients with known atrial fibrillation, and then knowing the bleeding risk of the procedure. Generally, patients considered at low risk for thromboembolic events actually don't require bridge therapy for elective colonoscopies, as studies have shown that peri-procedural bleeding rates are significantly higher than thrombotic rates in patients who receive bridge therapy.

However, we know that there are patients who are considered higher risk for thromboembolic events, and these are patients that have a mechanical valve prosthesis, recurrent thromboembolic events, patients who have CHADS VASc scores of 4 or greater, or patients who have atrial fibrillation with a recent CVA or TIA within the past three months; these are the high risk group of patients that bridge therapy would be warranted.

In these unique set of patients, conservative strategies for bridging though should be considered such as transitioning off low-molecular-weight heparin post-procedure when the INR approaches 2, rather than after. Another consideration should be switching patients from warfarin to a novel oral anticoagulant when appropriately indicated. So we know that the group of NOACs have shorter half-lives and they have more of a rapid achievement of therapeutic levels upon reinitiation, so these anticoagulants really require less time for discontinuation of anticoagulation and may be an advantage. So typically 48 hours of discontinuation of a NOAC is required prior to a procedure versus five days for something like warfarin. But I want to note that at this time there is really no data to support using NOACs as a bridging agent, but rather considering it as an alternative agent for warfarin, so that you are reducing the amount of time a patient is actually off of anticoagulation rather than considering it as a bridge.

Dr. Buch:
Thank you so much. How would you approach a patient who has had a recent drug-eluting stent with dual-antiplatelet therapy who now has a lower GI bleed?

Mr. Olsen:
We know that this is certainly something we've seen in clinical medicine more frequently than not due to the fact that patients are on dual-antiplatelet therapy with an increase of the use of drug-eluting stents, and many times patients are on triple therapy due to coexisting morbidities such as atrial fibrillation. But it's good to kinda understand the rationale behind the need for dual-antiplatelet therapy.

So patients who undergo placement of a drug-eluting stent require continuation of dual-antiplatelet therapy for 6 to 12 months to reduce the incidence of instant thrombosis. And when patients on dual-antiplatelet treatment present with lower GI bleed, the risk of discontinuing antiplatelet therapy really needs to be weighed against the risk of continued bleeding without interrupting that therapy. And

like anything, this requires a multidisciplinary approach since decisions may need to be individually based on the severity of bleeding.

For patients with life-threatening bleeding, dual-antiplatelet therapy should be discontinued but certainly for the shortest period of time possible in order to obtain hemostasis. For patients with non-severe bleeding and who are considered high risk for stent thrombosis, antiplatelet therapy is generally continued. And a scenario where this may happen is a patient who comes in with non-severe bleeding, perhaps a drop of their hemoglobin but their bleeding is not active, and they have had a recent drug-eluting stent within the last 30 days. The discontinuation of dual-antiplatelet therapy in this population of patients would be considered very, very high risk for instant thrombosis. But ultimately in patients whom we determine that antiplatelet therapy absolutely needs to be discontinued, there is no data on the optimal timing for reintroduction of these agents or the appropriate doses, doses that should be considered. But there are factors that we do take into account when restarting therapy and these factors include patient's hemodynamic status, their findings on a colonoscopy when this is a lower GI bleed, along with a lesion's risk for re-bleeding.

So we would generally restart antiplatelet therapy one to three days following hemostasis. Other strategies include changing patients who are currently being treated with either ticagrelor or Prasugrel to clopidogrel, as this has been shown to reduce re-bleeding risks in patients who present with upper GI bleeding.

Dr. Buch:
That's from the GI perspective. It's a very important thing for my gastroenterology colleagues to just realize that it's better to have a slight GI bleed or even a moderate GI bleed than have a major cardiac event, and that's a changing paradigm that we've realized in the last few years.

That's all the time we have for today. I really want to thank Professor Olsen for sharing his insights on some very difficult clinical scenarios.

Mr. Olsen:
Thank you very much for your time today.

Dr. Buch:
For ReachMD, this is Dr. Peter Buch. To access this episode as well as others from the series, visit ReachMD.com/gi-insights where you can Be Part of the Knowledge. See you next time!