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Severe GI Bleeds & Hemodynamic Instability: A Call to Action

ANNOUNCER:

Welcome to ReachMD. This medical industry feature, titled “Warfarin, Severe GI Bleeds & Hemodynamic Instability: A Call to Action” is sponsored by CSL Behring.

Here's your host, Dr. Jennifer Caudle.

DR. CAUDLE:

This is ReachMD, and I'm Dr. Jennifer Caudle. Joining me to discuss how to address and treat major GI bleeds brought on by warfarin, is Dr. Majed Refaai, a Professor in the Department of Pathology and Laboratory Medicine at the University of Rochester Medical Center.

Dr. Refaai, welcome to the program.

DR. REFAAI:

Thanks for having me.

DR. CAUDLE:

Before we begin, let's review some Important Safety Information.

ANNOUNCER:

KCENTRA®, Prothrombin Complex Concentrate (Human), is a blood coagulation factor replacement product indicated for the urgent reversal of acquired coagulation factor deficiency induced by Vitamin K antagonist (VKA—eg, warfarin) therapy in adult patients with acute major bleeding or the need for urgent surgery or other invasive procedure. KCENTRA is for intravenous use only.

Stay tuned for the complete Important Safety Information for KCENTRA throughout this podcast.

DR. CAUDLE:

So Dr. Refaai, to start us off, what can you tell us about the burden and causes of GI bleeding?

DR. REFAAI:

Overall, GI bleeds are associated with approximately 800,000 annual visits to the emergency department in the United States. This includes lower and upper GI bleeds.¹

While patients with upper GI bleeds are more likely to be hospitalized as compared to lower GI bleeds, it's been reported that incidence of lower GI bleeds has increased by 25 percent between 2006 and 2014.¹

We really don't know the exact reason behind this increase, but it may be related to the increased use of oral anticoagulants or the rise in average age of elderly populations.

DR. REFAAI:

In fact, one of the main causes of upper GI bleed is Peptic ulcer disease, which can be caused by use of medications that affect blood coagulation, such as anticoagulants, aspirin, and NSAIDs, along with medical conditions like gastritis, among others.²

As for lower GI bleeding, diverticulosis, inflammatory bowel disease, or infectious diarrhea, for example, could be some underlying causes.^{3,4}

DR. CAUDLE:

And at what point should clinicians be concerned about a patient's GI bleed?

DR. REFAAI:

It really depends on the severity of the bleed. The more severe, the more urgent action we need to take.

DR. REFAAI:

For example, minor bleeds are mostly self-limited and may not require hospitalization.^{4,5}

But patients with major GI bleeds often present with urgent, life-threatening hemodynamic instability and possibly hypovolemic shock.^{6,7}

This is mostly seen in major GI bleeds that originate in the upper GI tract, either in the esophagus, stomach, or duodenum. These are usually categorized based on anatomic or pathophysiologic factors, such as ulcers, vascular issues, trauma, or those due to tumors or portal hypertension or even from complications of some medications.⁵

Management of these cases includes discontinuation of the anticoagulant and immediately administering volume resuscitation, blood products and anticoagulation reversal agents as needed. Once the patient is stabilized, we may also perform an endoscopy to locate and identify the source of bleeding.^{8,9}

DR. CAUDLE:

Now, you mentioned hemodynamic instability, and I'd like to dig into that a bit more. What should physicians look for in this situation, and why is it so urgent?

DR. REFAAI:

Patients with a major GI bleed and hemodynamic instability don't have enough blood to maintain blood pressure in their circulation that is necessary to keep blood streaming into critical organs.^{8,10}

Physicians should look for increased heart rate, hypotension and anemia signs and symptoms like, chest pain, shortness of breath and pale skin.¹⁰⁻¹²

Hemodynamic instability can increase the risk of myocardial infarction, time spent in the ICU, and mortality, because poor perfusion may lead to organ damage and organ failure, while hemorrhagic shock may cause multiorgan failure and death.^{13,14}

So based off of that, it's clear that hemodynamic instability signals the need for urgent measures to control the bleed as quickly as possible.⁸

DR. CAUDLE:

Now going back specifically to GI bleed reversal, Dr. Refai, what should be the approach in this life-threatening situation?

DR. REFAAI:

As I mentioned earlier, for a patient with an acute, severe, ongoing GI bleed who's taking an anticoagulant such as warfarin, while we are stabilizing the patient hemodynamically, a reversal agent should be initiated according to the GI bleeding-specific guidelines.^{8,15,16}

DR. CAUDLE:

And can you briefly describe these guidelines?

DR. REFAAI:

Sure, for patients on warfarin presenting with a significant bleed and an INR, which stands for international normalized ratio, of greater than or equal to two, we should consider immediately administer prothrombin complex concentrate, or PCC for short.⁹ I've also seen some of these patients present with a heart rate of more than 100 beats per minute and blood pressure of lower than 90/60. And evidence has shown that PCC is superior to traditional plasma in reversing warfarin-related major bleeding.⁹

But we have to keep in mind that guidelines specifically mention a 4F-PCC,⁹ an example being KCENTRA[®], which is a concentrated coagulation factor product indicated as an urgent warfarin-reversal agent.

DR. CAUDLE:

Before we continue our conversation, let's review some additional Important Safety Information for KCENTRA[®].

ANNOUNCER:

WARNING: ARTERIAL AND VENOUS THROMBOEMBOLIC COMPLICATIONS

Patients being treated with Vitamin K antagonist therapy have underlying disease states that predispose them to thromboembolic

events. Potential benefits of reversing VKA should be weighed against the risk of thromboembolic events, especially in patients with history of such events. Resumption of anticoagulation therapy should be carefully considered once the risk of thromboembolic events outweighs the risk of acute bleeding. Both fatal and nonfatal arterial and venous thromboembolic complications have been reported in clinical trials and postmarketing surveillance. Monitor patients receiving KCENTRA and inform them of signs and symptoms of thromboembolic events. KCENTRA was not studied in subjects who had a thromboembolic event, myocardial infarction, disseminated intravascular coagulation, cerebral vascular accident, transient ischemic attack, unstable angina pectoris, or severe peripheral vascular disease within the prior 3 months. KCENTRA might not be suitable for patients with thromboembolic events in the prior 3 months.

DR. CAUDLE:

So let's switch gears and talk about urgent warfarin reversal through the lens of a hypothetical patient case. Dr. Refaai, can you walk us through this?

DR. REFAAI:

Of course. So William is a 72-year-old patient who presented to the emergency department after three days of GI distress, upper abdominal pain, nausea, vomiting, and dark stool, also known as melena, all which suggest a GI bleed.

William's medical history includes aortic valvular disease, high blood pressure, chronic kidney disease and renal failure, and congestive heart failure. So already he's at risk for fluid overload. His relevant medication history includes warfarin as well.

His initial physical examination and vitals revealed signs of anemia and hemodynamic instability, which potentially indicates reduced blood flow and oxygenation.

So we have to ask ourselves: are these signs and symptoms due to his cardiovascular issues or could they be GI-related issues? We also need to ask: how severe is his abdominal pain and where did it originate?

An emergent nasogastric aspirate was done and was positive for bright red blood, which further suggests an upper GI bleed.

The next steps in the management of this case included a full lab workup, imaging, and GI consults to confirm the clinical picture and to determine the severity of the bleed.

William's labs were significant for an elevated INR of 2.8, low hemoglobin of 9.6 mg/dL, and hematocrit of 30 percent.

DR. CAUDLE:

Thanks, Dr. Refaai, this is such an interesting case. Can you piece this all together for us? How was William diagnosed and treated?

DR. REFAAI:

With William's low blood pressure, hemoglobin, and hematocrit, which are all signs of early hemodynamic instability, management should be initiated immediately. If his bleeding wasn't quickly contained, he was at risk for hypovolemic shock.

In addition to the symptoms I mentioned earlier, we need to look for things like cold extremities with blueish discoloration of the skin, confusion, decreased urination, loss of consciousness, and restlessness, which are all clear signs of hemodynamic instability.^{10,12,17}

The question here is, how significant is INR correction in this hemodynamically unstable GI-bleeding case? And I think the answer is, "very significant, and it should be achieved quickly."

DR. REFAAI:

So to reverse the warfarin anticoagulation effect in his system, William was given 2500 factor IX units of KCENTRA® along with an IV infusion of 10 mg of vitamin K.

William was then transferred to the ICU to monitor his vitals, bleeding, and labs.

These efforts helped to normalize his INR to 1.2 within 30 minutes, and it was maintained around 1.3 over the next 24 hours. This allowed the GI intervention team to perform an upper GI endoscopy and cautery completely within a few hours of his admission, which stopped his bleeding.

DR. CAUDLE:

So it sounds like KCENTRA® was the right choice for this patient type. But what other considerations should physicians think about when choosing a reversal agent?

DR. REFAAI:

In my experience, I've seen many physicians choose plasma to reverse warfarin-associated bleeding, which until recently, was our standard reversal therapy.

However, plasma can pose risks of volume overload, particularly in hemodynamically unstable patients presenting with cardiac and/or renal insufficiency.¹⁸

In fact, a retrospective analysis of complications in 251 patients who received plasma for warfarin reversal showed that 20 percent of those patients experienced pulmonary complications. About 12 percent experienced transfusion-associated circulatory overload, seven percent experienced pulmonary edema, and one percent had a transfusion-related acute lung injury, which is the most fatal side effect of plasma transfusion.¹⁸

So it's important that physicians know we have another option, KCENTRA[®], for urgent warfarin reversal that shows superiority in rapid and sustained INR correction, as well as infusion time.¹⁹

In addition, the reversal guidelines of the American College of Gastroenterology and the Canadian Association of Gastroenterology Clinical Practice recommend against plasma administration for warfarin reversal and advise the use of 4F-PCC in patients on warfarin who are hospitalized for an acute GI bleed.²⁰

DR. CAUDLE:

Now Dr. Refaai, we're just about out of time, but before we close, what would you like to leave our audience with today?

DR. REFAAI:

I'd like to again stress the urgency around major GI bleeds, especially in hemodynamically unstable patients, as the risk for life-threatening complications is significant.^{13,14}

Also, KCENTRA[®] isn't just for intracranial hemorrhage as is commonly thought, and it's just as viable for major GI bleeds in my opinion.

As in William's case, speed matters. The faster we can reverse warfarin and correct INR to address a bleed, the faster we can initiate medical procedures, and the more we can avoid serious complications or death. This may also reduce ED, ICU, or overall hospital lengths of stay.

DR. CAUDLE:

That's a great way to round out our discussion on urgent warfarin reversal.

I'd like to thank my guest, Dr. Majed Refaai, for helping us better understand and manage major GI bleeds.

Dr. Refaai, it was great speaking with you today.

DR. REFAAI:

It's always a pleasure, thank you for having me.

DR. CAUDLE:

I'm Dr. Jennifer Caudle.

And please stay tuned to hear some Important Safety Information.

ANNOUNCER:

KCENTRA is contraindicated in patients with known anaphylactic or severe systemic reactions to KCENTRA or any of its components (including heparin, Factors II, VII, IX, X, Proteins C and S, Antithrombin III and human albumin). KCENTRA is also contraindicated in patients with disseminated intravascular coagulation. Because KCENTRA contains heparin, it is contraindicated in patients with heparin-induced thrombocytopenia (HIT).

Hypersensitivity reactions to KCENTRA may occur. If patient experiences severe allergic or anaphylactic type reactions, discontinue administration and institute appropriate treatment.

In clinical trials, the most frequent ($\geq 2.8\%$) adverse reactions observed in subjects receiving KCENTRA were headache, nausea/vomiting, hypotension, and anemia. The most serious adverse reactions were thromboembolic events, including stroke, pulmonary embolism and deep vein thrombosis.

KCENTRA is derived from human plasma. The risk of transmission of infectious agents, including viruses and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent and its variant (vCJD), cannot be completely eliminated.

Indications

KCENTRA[®], Prothrombin Complex Concentrate (Human), is a blood coagulation factor replacement product indicated for the urgent

reversal of acquired coagulation factor deficiency induced by Vitamin K antagonist (VKA—eg, warfarin) therapy in adult patients with acute major bleeding or the need for urgent surgery or other invasive procedure. KCENTRA is for intravenous use only.

Please see full prescribing information for KCENTRA.

To report SUSPECTED ADVERSE REACTIONS, contact the CSL Behring Pharmacovigilance Department at 1-866-915-6958 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

ANNOUNCER:

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