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BLOOD STOP DRUGS IN EMERGENCY MEDICAL CARE

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Abstract:

Dear reader, in this article you can get information about what drugs we can help faster if we use to provide first aid at the time of bleeding, one of the most frequent cases of the moment.

Keywords: Blood , Drug , Gastrointestinal , Thrombin

Your EMS flight crew is dispatched by rotor to a remote hospital in the Great Basin Desert for a patient with gastrointestinal (GI) bleeding. The patient was brought in by her grandson. She was vomiting blood as well as suffering from bloody diarrhea.

On arrival, you find an 80-year-old female sitting up in a hospital bed, although she's extremely weak. She has a Glasgow coma scale (GCS) of 15 and states she's been throwing up blood all day.

She appears pale but is in no obvious distress. Her vital signs are a heart rate of 100 with regular pulse; blood pressure 60/35 mmHg; respiratory rate of 20; and $SpO_2$of 94% with poor waveform on 2 L/min via nasal cannula. The patient's history is limited to atrial fibrillation and hypertension.

Her nurse informs you that she's received 80mg Protonix (pantoprazole) and a liter of normal saline (NS). Given the patient's active GI bleed, her current blood pressure, and the 1.5 hour-plus flight to the receiving facility, you decide it's appropriate to request the hospital's only two units of packed red blood cells (PRBCs).

You load the patient into the helo without difficulty. As you begin transport, you find yourselves facing a strong headwind. Your pilot says that because of this you'll have to stop for fuel on the way to complete transport.

You and the crew put your heads together and decide the best course of action is to set down at your home hospital pad. This will take you off course from your receiving hospital, but your home hospital has fuel and additional blood products available.

The decision will add approximately 15 minutes to the already long transport, but no other facilities can offer you what this one has. You call ahead to have two units of fresh frozen plasma (FFP) at the ready.

While on the way to get fuel and FFP, you place the patient on nasal EtCO2 and obtain an initial reading of 20 mmHg. You immediately begin transfusing the first unit of PRBCs.

The patient's history of atrial fibrillation gives you pause for thought and you look more closely through the history and physical examination paperwork you received from her nurse. Your concern is that this patient may be anticoagulated-a measure to prevent clots from forming in her less-than-rhythmic atria, but also complicating her primary diagnosis of a GI bleed.

The paperwork says she's on warfarin. The page with hospital labs tells you her international normalized ratio (INR) is 5.0 (1.0 is normal; 2.0-3.0 is therapeutic for anticoagulated patients). You also come to find out that the sending facility did, in fact, give the patient vitamin K (10 mg IV), despite this not being mentioned in the hand-off report you received.

You note that the patient's blood pressure begins to respond to the PRBCs as well as a second liter of NS. Her systolic blood pressure is now in the 80s and her $EtCO_2$ is 28 mmHg.

The aircraft lands without incident to refuel and two units of thawed FFP are ushered out to the aircraft. After the first unit of PRBCs has finished, you immediately hang one of the units of FFP.

The helicopter lifts. The patient subsequently states to you that she doesn't feel well and begins projectile vomiting. Everything from the monitor to the radio to the sun visor on your helmet is painted in partially digested blood.

You note that your patient has become less responsive, at which point airway protection now becomes paramount. Clicking up the visor, you locate and reach for your only clean surface to work on: a spare blanket. The setup for rapid sequence intubation

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moves along smoothly as you preoxygenate, induce with ketamine, paralyze with rocuronium and intubate.
The patient is placed onto the ventilator before any notable desaturation occurs. Your partner then inserts an orogastric tube and attaches it to the suction unit, yielding a steady and voluminous return of blood.
Continuing down the transfusion pathway (and cleaning up where you can), you deliver the remaining two units of blood products, hoping to reverse your patient's coagulopathy and perhaps replace some small amount of what she's lost. You add to that a dose of IV calcium gluconate.
In spite of the staggering amount of blood collecting in the suction canister and soaking into the aircraft upholstery, the patient's vital signs seem to improve.
On a sullied monitor screen, you note that her heart rate is 90; blood pressure appears to have climbed to 135/85 mmHg; EtCO2 is 37 mmHg; and her oxygen saturations are holding and reaching as high as 98%, so you can begin to titrate her FiO2 down. With attention to the finishing touches, the patient is given further sedation as well as analgesia to ease her through her ride on the vent.
Thankfully, the flight proceeds without further incident as does your final handoff to staff at the receiving hospital. Repeat labs done on admission at the bedside find your patient's INR to have reversed course; now a sterling 1.5.
In one final moment, you watch from the ED hallway as your patient is wheeled away to the operating room. She's found to have a bleeding ulcer, which is cauterized.
The good news eventually comes that she was extubated several days later and discharged within a week to a skilled nursing facility … which is meaningful to hear, because you feel like it took nearly that long to clean the aircraft.

DISCUSSION

There are few cases more challenging in EMS than the critical geriatric patient. These become all the more so when we're handed the long list of medications they may-or may not-have been taking, and then left asking how our treatment plan should now change. Among those medications it's not uncommon to find blood thinners prescribed specifically to help protect the patient to some extent from the risk of stroke, emboli and coronary events.
Within this broader realm of pharmacology, the prescribed medications fall into one of two larger groupings: antiplatelet agents or anticoagulants. The former group includes medications such as aspirin, clopidogrel (Plavix), dipyridamole (Persantine), ticagrelor (Brilinta) and ticlodipine (Ticlid). The latter constitutes a list we might find just as familiar, with names such as warfarin (Coumadin or Jantoven), enoxaparin (Lovenox), dalteparin (Fragmin), rivaroxaban (Xarelto), apixaban (Eliquis) and dabigatran (Pradaxa).
Collectively, these act on the body to thin the blood along a number of different pathways. In order to understand how to deal with each of these medications in an emergency setting, we need to first understand how each of them contribute to clot formation.
An article on the coagulation cascade could fill an entire journal with the minutiae involved, and attempting to memorize every nuance could have you forgetting other important details in life such as birthdays and the location of your car keys. In this case, we focus on aspects of the clotting cascade that relate to the practicality of our jobs.
A blood clot consists of two components: platelets and cross-linked fibrin strands. Platelets will gather initially at the site of any tissue injury or bleeding, but in order to bind together and form a stable blood clot they require something more. A meshwork of fibrin is necessary for clot formation, and it's what we have to blame for the confusing array of factors, proteins and other mediators that so many of us find intimidating.
These two requirements for blood clotting-platelets and cross-linked fibrin strands-are the reason there are two classes of prescribed medications to work against coagulation. Antiplatelet agents (e.g., aspirin, Plavix, etc.) target platelets specifically. Meanwhile, anticoagulants act at a number of different points on the formation process of the fibrin meshwork.
To further appreciate the steps that lead to fibrin activation and cross-linking, we should take a step back. With any vessel damage and bleeding, there's also activation of an enzyme called tissue factor (otherwise known as factor III), in addition to platelet activation. This sets off the extrinsic pathway in the coagulation cascade.
A number of other factors are subsequently involved and activated, leading us into the common pathway of the clotting cascade. The common pathway begins with factor X which, by way of its activation (Xa), catalyzes the formation of thrombin (factor IIa), fibrin (IIa), and finally a stable fibrin meshwork at the site of bleeding. Within this sequence, the activation of prothrombin (2) to thrombin (2a) triggers a separate and accelerating process known as the intrinsic pathway. This chain of reactions, involving still other clotting factors, all the more gainfully activates factor

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X in a positive feedback loop, leading to substantially greater thrombin and fibrin formation.

The positive feedback thrombin loop involves numerous other factors (I-XIII) as well as their activated forms), however, we'll limit ourselves to briefly mentioning only two other players in the coagulation cascade to the treatments placed at our fingertips. The first is vitamin K and the second is calcium. Each plays the role of a necessary cofactor in activation of specific clotting factors within both the extrinsic and intrinsic legs of the coagulation cascade, as well as along the common pathway (targeting factor Xa and thrombin). In the absence of either vitamin K or calcium, a patient can suffer from serious coagulopathy.

Warfarin, perhaps the most commonly seen anticoagulant in our modern-day pharmacopeia, specifically acts to reduce the amount of vitamin K available for use in the clotting cascade, and subsequently interferes with coagulation, as it did in this case.

Also in the case of this patient, a dose of calcium was given to the patient before providers administered a fourth unit of blood products. This was done because of blood product administration. Each unit of PRBCs (also FFP or whole blood) contains a preservative called citrate which acts to keep the product from clotting while in cold storage and awaiting transfusion. Citrate is a chelating agent that serves to bind up available calcium and consequently prevent it from accelerating the clotting process. Once this citrate is released into the patient's bloodstream during a transfusion, it'll do the same to calcium circulating within the patient's own blood.

In transfusions after many units of blood have been given, the patient's ability to form clots can be derailed by the increasing amounts of citrate present, leading to a paradoxical coagulopathy caused by our attempt to treat the hemorrhage. Administering IV calcium helps to augment and/or replace the free calcium that's been bound up by citrate.

The medication-assisted manipulation of one's clotting cascade with prescriptions can go well beyond vitamin K and calcium. Low- molecular-weight heparins, a long-utilized class of blood thinners, include household names like Lovenox and Fragmin. They act by accelerating the already-present processes that work to inhibit and thus counterbalance the clotting actions of factors Xa and thrombin.

Newer generations of drugs are also now targeting and inhibiting the action of specific coagulation factors directly; as in the case of Pradaxa with thrombin as well as Xarelto and Eliquis with factor Xa. These offer the possibly improved benefit with decreased risk of complications by virtue of their novelty over warfarin, however they're not without their own risks of bleeding or complications.[1]

We look to lab values to gain a sense for how much of an effect an anticoagulant or antiplatelet medication has exerted on a patient's blood. For clinical assessment of the patient's anticoagulant status in the austere emergency setting we most often refer to the INR, a standardized metric derived from another, less-objective test called the prothrombin time, which measures time to coagulation down the extrinsic and final common pathways. The INR quantifies and calibrates a patient's blood specimen to a normalized (control) sample as well as the means of lab measurement. When encountering a patient who takes anticoagulants, we find an INR that's elevated beyond its normal threshold of 1.2.[2,3]

Antiplatelet agents, on the other hand, have no effect on the INR, leaving us with no means of rapid, standardized testing for them in the frontline emergency setting until recently.[4] With the advent of newer and more potent antiplatelet drugs, technology-assisted point-of-care methods for assessing platelet function, such as thromboelastography (TEG) mapping are showing promise in EDs, but are still in the early phase of adoption and have yet to spread to the smaller community, rural and field settings.[4]

TAKE-HOME POINTS

Reversal of drug-induced coagulopathies can be an important part of treating an upper GI bleed or any other type of hemorrhage in the prehospital setting. Note that patients with liver disease and bleeding varices can be intrinsically coagulopathic, and the correction of these clotting disorders is beyond the scope of this article. Be aware that we sometimes encounter patients with GI bleeding who aren't taking warfarin yet still have significantly prolonged INRs due to pre-existing hepatic problems.

For hemodynamically unstable patients taking warfarin, though, our first choice for reversal should be prothrombin complex concentrate (PCC). PCC is standardized by the amount of factor IX contained per unit, though also consisting of factors II and X. A more recently FDA-approved 4-factor PCC formulation called Kcentra contains factor VII as well. PCC is administered IV, usually at the dose of 25-50 IU/kg. It's superior to FFP in that it can be reconstituted in far less volume for equivalent dose; it's processed with better antimicrobial precautions; it can be administered regardless of blood type without the concern for transfusion reactions; and it can be

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infused more rapidly with a quicker response anticipated in the patient's condition.[5-7]

FFP can be used as an alternative when PCC isn't available, as there's still insufficient data to suggest that PCC reduces mortality compared to FFP.[8] The recommended dose of FFP is an IV infusion of 15 mL/kg, which translates to about 3-4 units of FFP.

Looking for signs of reversal, the patient's INR can be rechecked 20-30 minutes after infusion of PCC, or for FFP recheck at an hour. In addition to one of these agents, the standard treatment regimen also calls for vitamin K (Aquamephyton) to be infused 5-10 mg IV over 30 minutes.

For stable patients who have significant bleeding, vitamin K, with a longer onset of action (1-2 hours), can be used as a sole agent since time-sensitive reversal isn't an immediate concern.[9]

Newer direct oral anticoagulants are a much tougher proposition for reversal. There are no high-quality studies that have proven strategies for reversal of these agents. The advantage of these agents, however, is that they have short half-lives, and so a strategy to halt the offending agent becomes key to reversal. Gastric lavage along with activated charcoal can be used, provided that the medication was taken in the prior 2-3 hours.[9]

Dabigatran is a direct thrombin inhibitor for which there's a novel reversal agent: idarucizumab (Praxbind), which is approved for use in patients with life-threatening or uncontrolled bleeding. It's been found to achieve consistent and near-total reversal of dabigatran shortly after infusion.[10] The recommended dose is 5 grams. Another laboratory test, the activated partial thromboplastin time (aPTT), can be used to get a relative sense for improvement in coagulopathy on dabigatran, but isn't reliable to measure the extent of the coagulopathy.[9]

In the absence of Praxbind, hemodialysis has proven the most effective option for reversal of dabigatran's effects via removal. There's no role for PCC in dabigatran reversal.[11]

Factor Xa inhibitors Xarelto, Eliquis, and Savaysa (edoxaban) have no specific FDA-approved antidotes. Treatment strategies call for the administration of 50 IU/kg PCC with the caveat that there's no high-quality data demonstrating clinical efficacy of this strategy in GI bleeds.11 Again, consider FFP if PCC isn't available. There are, however, at least two reversal agents in development for factor Xa inhibitors that are moving toward FDA approval.[12]

For heparin and low-molecular-weight heparins, we administer protamine sulfate for reversal. Dosing is 1 mg for every 100 units heparin administered in the last 2-3 hours. For Lovenox (enoxaparin), give 1 mg protamine for every 1 mg enoxaparin taken within the last 8 hours. Finally, for Fragmin (dalteparin), give 1 mg per 100 units taken orally over the last 8 hours.[13] Keep in mind that bradycardia and hypotension are common side effects to protamine so it's best to administer slowly over 5-10 minutes.[13]

There are no proven reversal agents for antiplatelet agents (e.g., aspirin, Plavix, Ticlid, etc.). If the patient presents with signs of coagulopathy after use of one or several of these, treatment can begin with 5 units of platelets to offset typical antiplatelet dosing.[14]There's also early evidence for use of desmopressin (DDAVP) at 0.3-0.4 mg/kg to increase platelet adhesiveness and improve outcomes in this patient population, though more research is needed before definitive recommendations can be made.[15,16]

CONCLUSION

The use of blood thinners has become more common in the general population and the number of anticoagulant and antiplatelet medications available on the market have also grown. Although these drugs can prevent patients from forming clots and stave off medical maladies such as strokes, deep venous thromboses and pulmonary emboli, their complications will continue to be an issue in the setting of hemorrhage. Even an uncontrolled nosebleed can be lethal with the wrong mix of these medications.

Becoming familiar with anticoagulants and their respective reversal strategies will enable providers to quickly and accurately administer the proper reversal agents. Therefore, it's imperative that providers obtain a good medication history to drive treatment in the right direction. Skipping this vital step could lead to delaying definitive care, which might be fatal. Whenever we find ourselves with a bleeding patient-no matter trauma or medical, young or old-we should *always* be asking, "Is my patient on any anticoagulation therapy?"

Patients may not understand the connection between their blood thinners and the present trauma or illness, but as care providers we absolutely must. And if improving our expediency to identify and treat these patients requires us to revise our trauma alert practices or criteria, then let us do so. As in this patient's case, identification of bleeding in the setting of coagulopathy can expedite definitive treatment and help to save a life.

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