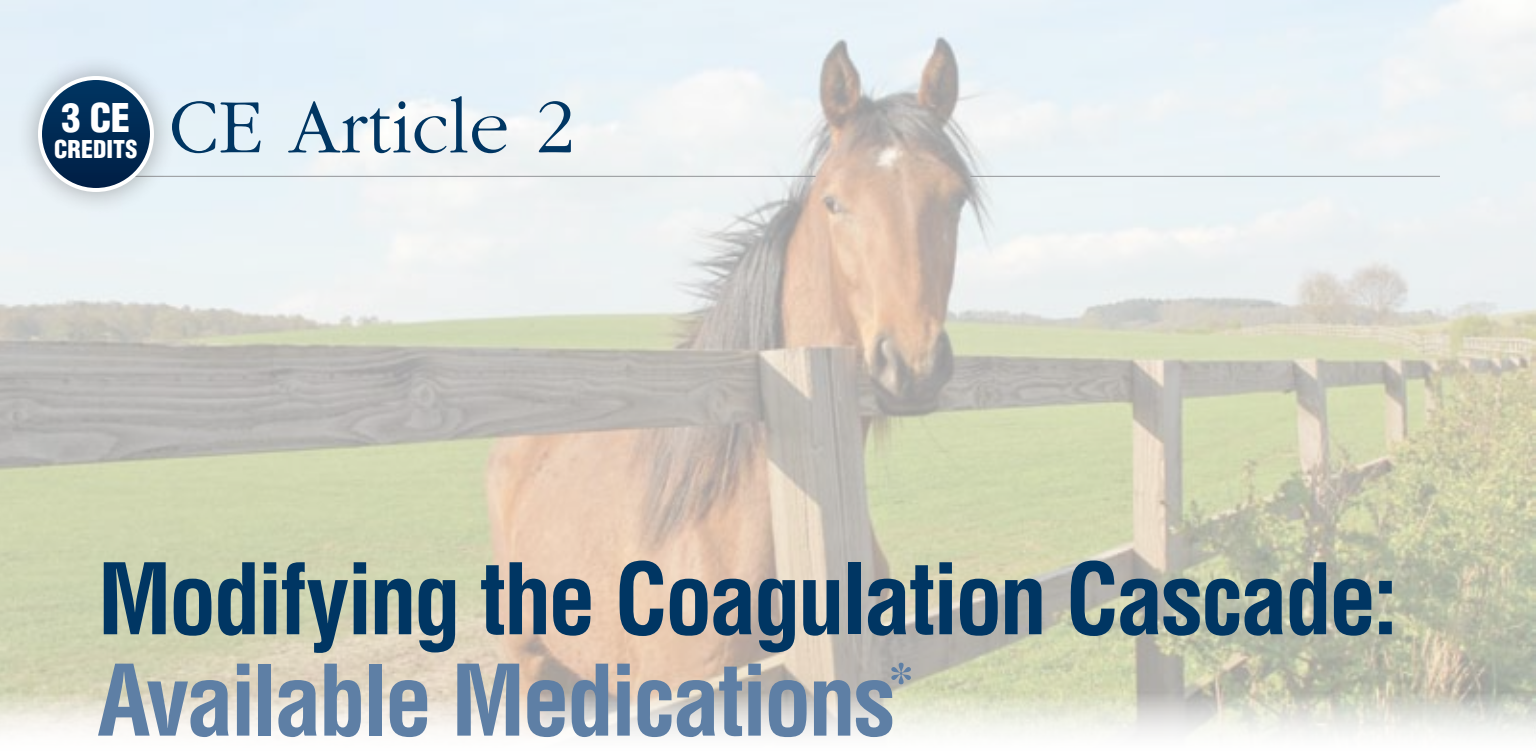

3 CE CREDITS CE Article 2

Modifying the Coagulation Cascade: Available Medications*

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Abstract: *Equine practitioners require a basic knowledge of the coagulation cascade to effectively diagnose and treat many primary diseases. With this knowledge, practitioners can administer adjunctive medications to horses to promote an anti- or procoagulant state. Among the anticoagulants, heparin has received the greatest attention in equine medicine. However, other anticoagulants, such as aspirin and warfarin, have also been used in horses. Alternatively, medications such as tissue plasminogen activator and urokinase have been administered to foals with thromboembolism. In addition, medications such as aminocaproic acid and formalin have been administered to horses to promote hemostasis. While the benefits of many of the medications used for these purposes in horses remain unsubstantiated, numerous case reports and reviews have recommended these therapeutic options in horses. Thus, appropriately administered medications that modify the coagulation cascade may be beneficial prophylactic or therapeutic choices in certain instances.*

At a Glance

*A companion article titled "Hemostasis" was published in the March 2009 issue.

Coagulopathies are occasionally encountered secondary to various disease processes in equine medicine, especially in critically ill equine patients (**BOX 1**). At times, coagulopathies can result in performance-limiting (e.g., laminitis) or life-threatening (e.g., disseminated intravascular coagulation [DIC]) conditions. Although no single medication is likely to eliminate these complications, various medications are available to modify the coagulation system to promote or retard hemostasis in horses. Many of the medications discussed in this article have limited experimental evidence to support positive clinical efficacy and use in horses. However, these medications have been used in an attempt to treat various disease processes in multiple anecdotal reports. This article summarizes the mechanism of action and potential applications of some of the more commonly used anti- and procoagulant medications in horses.

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- Therapeutics in Practice: Acute Blood Loss (March 2008)
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Anticoagulants

Among the anticoagulants, heparin has been used most widely in equine medicine in an attempt to prevent or control the progression of many diseases, such as postceliotomy intestinal adhesion formation, DIC, acute laminitis, and vessel thrombosis.

Unfractionated Heparin

Unfractionated heparin (UFH) is a heterogenous mixture of glycosaminoglycan chains that vary in molecular weight from 3000 to 40,000 daltons.[1,2] The mechanism of action of heparin includes its ability to bind to antithrombin, resulting in a conformational change of the reactive center of antithrombin and acceleration of the interaction between antithrombin and activated factor X (Xa) or thrombin by approximately 1000 times.[1] Subsequently, inactivation of factor Xa and thrombin occurs, inactivating various stages of the coagulation cascade. The interaction between heparin and antithrombin is mediated by a pentasaccharide sequence in the heparin chain.[1] To inhibit thrombin, the heparin chain must be long enough (at least 18 saccharide units) to bind and form a complex with antithrombin and thrombin (**FIGURE 1**).[1,2] Heparin also inactivates factors IX, XI, and XII and stimulates plasminogen activator activity. After inactivation of factor Xa and thrombin, heparin dissociates from the complex and is again biologically available.[2,3]

Endogenous heparin is produced by mast cells in most mammalian tissues, with the highest concentrations produced in the lungs, liver, and intestine.[2] In addition, heparan sulfate is located on endothelial cell surfaces and promotes activation of antithrombin.

UFH is highly bound to plasma proteins, macrophages, and endothelial cells, which act as storage pools. When these pools become saturated, free heparin is available in plasma.[2,3] Because of these pharmacokinetic variables, individual and dose-related variations in efficacy may occur with the use of UFH.

Adverse effects of UFH administration in horses include thrombocytopenia and heparin-induced agglutination of erythrocytes.[2] Less frequent complications reported in horses include hemorrhage and pain at injection sites.[2,4] Protamine sulfate is a heparin antagonist and has been used in people (1 mg of protamine sulfate per 100 to 150 IU of heparin) to ameliorate untoward effects of heparin therapy.[2,5] Protamine competes with antithrombin for binding to heparin; because protamine has a stronger affinity for heparin, antithrombin is dissociated from the heparin–antithrombin complex, which reverses the anticoagulant function of heparin.[5] Protamine has additional effects, such as inhibition of factor VII activation of the extrinsic pathway, but its use should be judicious because profound hypotension, vasodilation, reflex tachycardia, and idiosyncratic fatal reactions have been reported in people.[2,5,6]

Heparin therapy has been used to treat various disease processes in equine medicine, but its true efficacy in clinical situations is unknown. Heparin has been administered intraperitoneally and systemically to prevent intestinal adhesion formation in horses—a complication that may increase morbidity and mortality after abdominal surgery.[7] Adhesion formation results from an imbalance between fibrin deposition and fibrinolysis.[7] The normal response to intraabdominal injury and inflammation involves the production of serofibrinous exudate by peritoneal mesothelium, deposition of a fibrin matrix, and release of tissue factor, thereby activating the extrinsic pathway of coagulation.[7–9] Cross-linked fibrin forms fibrinous adhesions; fibroblasts and endothelial cells subsequently infiltrate

BOX 1.

Clinical Signs of Coagulopathy

When performing venipuncture or inspecting indwelling intravenous catheters, clinicians or technicians should examine the patient for the following clinical signs of coagulopathy:

- Hematoma formation
- Prolonged or excessive bleeding at venipuncture site
- Thrombophlebitis
- Petechial or ecchymotic hemorrhage of mucous membranes (oral, vulvar)
- Epistaxis
- Thrombosis of veins or arteries (digital, brachial, aortoiliac)
- Hemarthrosis
- Intracavitary bleeding (abdominal or thoracic cavity)
- Soft tissue bruising
- Melena

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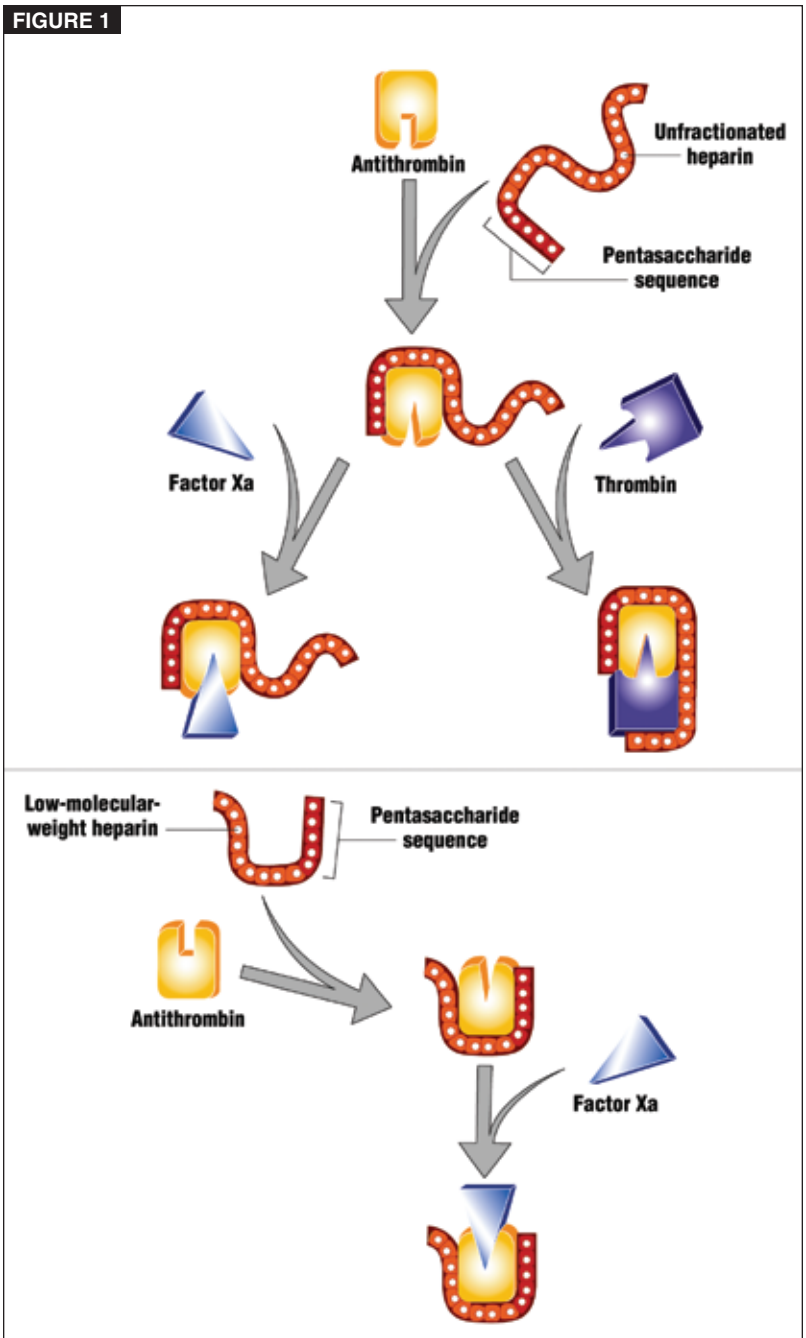
Heparin therapy has been used to treat various disease processes in equine medicine, but its true efficacy in clinical situations is unknown.

FIGURE 1



The pentasaccharide sequences of unfractionated heparin (*upper image*) and low-molecular-weight heparin (LMWH; *lower image*) bind to antithrombin, resulting in a conformational change in the reactive center of antithrombin. This conformational change accelerates the interaction of antithrombin with, and the inactivation of, factor Xa. In contrast, accelerated inactivation of thrombin by antithrombin requires the formation of a ternary heparin–antithrombin–thrombin complex, which can be formed only by chains that have at least 18 saccharide units. This explains the limited inhibitory activity of LMWH against thrombin compared with that of unfractionated heparin. (Adapted with permission.[1])

these adhesions, forming granulation tissue in response to the original mesothelial defect.[8] Under normal conditions, fibrin strands and fibrinous adhesions are lysed via local peritoneal fibrinolytic activity before fibrous maturation occurs.[7–9] More specifically, peritoneal mesothelial cells release tissue plasminogen activator (TPA), which subsequently activates plasminogen to plasmin, a natural fibrinolytic.[10] Intestinal ischemia, inflammation, distention, and trauma may suppress normal peritoneal fibrinolytic activity, thus predisposing a horse to adhesion formation following intestinal injury (colic) and abdominal surgery.[7]

Heparin therapy may facilitate decreased thrombin formation and the conversion of fibrin to fibrinogen, thereby decreasing fibrous adhesion formation. In addition, stimulation of TPA activity by heparin may enhance fibrinolysis.[7] Positive results of heparin therapy have been experimentally demonstrated in an ischemia–reperfusion model in ponies, but clinical studies have produced mixed results.[9,11] In the experimental ischemic bowel model, three of four control ponies developed multiple intestinal adhesions in response to ischemia, whereas only one of four heparin-treated (40 U/kg IV once at surgery, then 40 U/kg SC q12h for 48 hr) ponies developed a single adhesion. The results of this study have been used to suggest the use of low-dose heparin to prevent intestinal adhesions.[9] In another study involving 33 horses that underwent exploratory celiotomy, no significant differences were detected between the control group and heparin-treated (66 U/kg SC q12h for 72 hr) group regarding complications (fever, ileus, jugular vein phlebitis, acute laminitis) or survival rates.[11] Because of the variety of intestinal lesions reported, the cases selected may have had insufficient intestinal injury or peritoneal inflammation to benefit from heparin therapy. Therefore, the study was unable to evaluate the effect of heparin administration on intestinal adhesion formation. A more recent investigation in foals demonstrated intestinal adhesion formation in three of four foals treated with heparin (80 U/kg SC q12h for 72 hr), while adhesions were not observed in foals treated with dimethyl sulfoxide or the combination of flunixin meglumine and antimicrobials. These results suggest that heparin provides no benefit in preventing intestinal adhesions

Heparin has been administered in an attempt to reduce multiple complications in horses, including intestinal adhesions, disseminated intravascular coagulation, laminitis, and thrombophlebitis. The use of low-molecular-weight heparin may be associated with fewer adverse affects than the use of unfractionated heparin.

in foals.[12] Heparin (30,000 to 50,000 U) has also been added to 10 L of lavage fluid and administered intraabdominally after celiotomy to prevent intestinal adhesion formation, but the true efficacy of heparin in this situation is unknown.[10]

Heparin therapy may also be warranted for treating DIC. A brief review of the pathogenesis of DIC follows; more information is available elsewhere.[13] DIC can be described as widespread activation of the coagulation system, resulting in a procoagulant state with systemic thromboses and secondary diffuse hemorrhage throughout the body. DIC is not a primary disease but is secondary to pathologic conditions such as sepsis, localized infections, acute gastrointestinal (GI) disease (colic), colitis, neoplasia, trauma, hemolysis, hepatic or renal failure, vasculitis, and endotoxemia in horses.[14,15] While DIC is not always associated with these disease processes, in certain situations, the primary disease causes inappropriate overactivation of the coagulation cascade with subsequent production of fibrin and, ultimately, thrombotic occlusion of small and midsize vessels.[13] Thrombosis causes varying degrees of organ dysfunction or failure. Clinical manifestations of DIC in an individual horse depend, in part, on the nature, intensity, and duration of the initial stimulus and concentration of endogenous anticoagulants.[14,15] Concurrent suppression of anticoagulants such as antithrombin, protein C, and tissue factor–pathway inhibitor also contributes to DIC and delayed fibrinolysis.[13] Decreased plasma antithrombin, a major anticoagulant, is observed in people[13] and horses[14] during DIC, resulting from impaired synthesis of antithrombin and degradation by elastase released from activated neutrophils. Simultaneously, spontaneous hemorrhage may occur, resulting from the consumption and depletion of platelets and coagulation proteins.

DIC has been well documented in horses; the most common initiators are acute GI disease, such as strangulating intestinal obstruction, enteritis, colitis, and bacterial septicemia.[14–16] Endotoxemia is a common underlying pathophysiologic trigger of the inflammatory and coagulation cascade in both instances.[17,18] Addressing the primary disorder is crucial to treating DIC. Because obstruction of the microvasculature by microthrombi may result in organ (e.g., GI, renal) dysfunction or failure, the use of heparin has been suggested as a preventive therapy to decrease the incidence of thrombus formation. Controversial in human and veterinary medicine, the rationale for heparin therapy for DIC is based on inactivation of thrombin and factors Xa and XIa, which may prevent further conversion of fibrinogen to fibrin, thus reducing microthrombus formation.[19]

To date, controlled prospective studies that demonstrate efficacy of heparin in treating DIC in horses are lacking. In one study involving 23 horses with colic and DIC, a greater proportion of survivors (seven of eight) were administered heparin (40 to 90 U/kg SC q8h) compared with horses that died (nine of 15), but this finding was not statistically significant.[14] Heparin therapy used in conjunction with plasma therapy has been suggested if antithrombin activity is progressively decreasing or is less than 60% of normal values.[14,20] The addition of 400 U of heparin per liter of fresh-frozen plasma may activate antithrombin and inhibit coagulation protein activation when administered to horses in a hypercoagulable state.[20] However, studies in septic people have found that antithrombin therapy improved survival, whereas the combination of antithrombin and heparin had no benefit in terms of

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Decreased plasma antithrombin, a major anticoagulant, is observed in people and horses during DIC, resulting from impaired synthesis of antithrombin and degradation by elastase released from activated neutrophils. Addressing the primary disorder is crucial to treating DIC.

survival.[21] Furthermore, heparin may partially interfere with some of the antiinflammatory effects of antithrombin.[22] Additional studies in horses and people are needed before the effects of concomitant administration of heparin and antithrombin are fully understood.

Laminitis is another serious and debilitating disease with multiple causes and severities. Although the pathogenesis of equine laminitis is incompletely understood, coagulopathy and occlusion of digital vessels by microthrombi may play a role in the development of some cases of acute laminitis.[17,23] As noted above, conditions such as enterocolitis, colic, DIC, and other disorders involving endotoxemia may increase the incidence of thromboembolism in horses.[17] Thus, heparin has been used in efforts to prevent the development of thrombus formation and decrease the incidence of laminitis in certain clinical settings. An early study demonstrated a decreased incidence of lameness and rotation of the third phalanx in horses with carbohydrate-induced laminitis that were treated with heparin.[24] However, in another retrospective study of 71 horses that required abdominal surgery for small intestinal disorders, no difference in the incidence of laminitis was detected between untreated horses and horses treated with heparin.[25] However, a further retrospective study demonstrated a decreased incidence of laminitis associated with proximal enteritis in horses treated with heparin (0% [none of 12] developed laminitis) compared with horses that were not treated with heparin (29.8% [31 of 104] developed laminitis).[26] Differences in disease processes, heparin dose, and timing of administration; concurrently administered medications; and small sample size may explain some of the differences noted between these studies.

Phlebitis or thrombophlebitis can occur secondary to neonatal septicemia or as a sequela of severe GI, pulmonary, or systemic disease in horses.[27,28] Systemic coagulopathies, injury to the vessel wall (e.g., an indwelling intravenous catheter, repeated venipuncture), type of catheter material, type(s) of intravenous medications administered, and blood stasis may predispose horses to thrombophlebitis.[27,29] Prompt removal of intravenous catheters, avoidance of venipuncture, hydrotherapy, and topical antiinflammatory salves (e.g., dimethyl sulfoxide gel; 1% diclofenac sodium [SURPASS, IDEXX Laboratories]) frequently halt the progression of thrombophlebitis, particularly when instituted at the onset of clinical signs of blood vessel irritation and inflammation (palpable thickening of the vein, pain, swelling, exudation, increased resistance to catheter flow).[29] The clinician can also consider the use of anticoagulants, such as heparin, in equine patients in a hypercoagulable state. Heparin is ineffective at dissolving existing thrombi but may prevent thrombophlebitis or further extension of existing thrombi.[17,29] Although low-dose heparinized saline (10 U/mL of saline) is routinely used to flush catheters, clinicians may consider using systemic doses of heparin (20 to 40 U/kg SC q12h) to help prevent or treat thrombophlebitis.[17]

Thrombosis of central and peripheral vessels is a possible complication of sepsis in foals and severe infectious diseases in adult horses and warrants a guarded to poor prognosis.[27,30] Thrombosis of the bowel wall subsequent to severe infectious colitis and pulmonary thromboembolism as a sequela of necrotizing pneumonia have also been reported in horses.[27,31] Thrombolytic agents have been used in a foal with vessel thrombosis.[32] Aggressive treatment of the primary disease coupled with prophylactic administration of anticoagulants such as aspirin or heparin may help prevent vessel thrombosis, but prospective clinical trials are needed. Heparin therapy has been used in septic humans and a foal and may decrease the incidence of thromboembolic disease in humans.[32,33] In addition, adult horses with low antithrombin activity may be administered heparin (40 U/kg) preincubated with fresh-frozen plasma to provide anticoagulant proteins, and this treatment has been suggested to help prevent GI thrombosis secondary to systemic coagulopathies.[27]

Low-Molecular-Weight Heparin

The use of low-molecular-weight heparin (LMWH) has gained popularity in human and veterinary medicine because the drug has better bioavailability, a longer plasma half-life, a more predictable response, and decreased adverse effects compared with UFH.[4,34] LMWH has the ability to bind with antithrombin and inhibit factor Xa, but because of the small molecular size of the drug, fewer than half

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The use of low-molecular-weight heparin has gained popularity in human and veterinary medicine because the drug has better bioavailability, a longer plasma half-life, a more predictable response, and decreased adverse effects compared with unfractionated heparin.

of LMWHs have molecules that are of sufficient length to bind to both antithrombin and thrombin; therefore, these LMWHs have lower activity against thrombin (**FIGURE 1**).[1]

LMWH has been investigated in horses at a dose of 50 U/kg SC q24h and has demonstrated adequate therapeutic/prophylactic plasma concentrations after the first administration.[4] In addition, no agglutination of erythrocytes and no significant change in packed cell volume, hemoglobin concentration, or platelet counts occurred in the LMWH group compared with the UFH group.[4] One study that compared the use of UFH versus LMWH in horses with colic demonstrated a decreased incidence of jugular vein changes (partial thrombosis or thickening of the wall of the jugular vein) in horses administered LMWH (four of 16 [25%]) compared with those administered UFH (eight of 13 [61.5%]) after surgery.[34] Another equine study investigated the pharmacokinetic properties of two LMWH preparations (dalteparin and enoxaparin) and suggested doses of 50 U/kg SC q24h of dalteparin or 40 U/kg SC q24h of enoxaparin as a prophylactic anticoagulant treatment.[35] Higher doses (100 U/kg SC q24h of dalteparin or 80 U/kg SC q24h of enoxaparin) were suggested for treating horses considered to be at high risk for developing thrombotic disease.[35] Furthermore, a clinical study that used 50 U/kg SC q24h of dalteparin in horses being treated medically or surgically for colic demonstrated fewer adverse effects compared with the use of UFH.[34]

A recent study has investigated the use of another anticoagulant medication, recombinant hirudin, in healthy horses.[36] In people, hirudin is primarily used to prevent or treat arterial or venous thrombosis. Hirudin directly and irreversibly inhibits free and fibrin-bound thrombin, independent of antithrombin activity. No adverse reactions or significant changes were noted in general behavior, bleeding tendency, or hematologic or biochemical parameters in healthy horses administered hirudin.[36] For prophylaxis and treatment of thrombotic disease in horses, doses of 0.5 and 1 mg/kg SC q12h, respectively, of hirudin were recommended.[36] However, the use of hirudin in clinical cases needs further investigation.

> Limited information on the use of thrombolytic medications (e.g., tissue plasminogen activator) is available in horses. However, thrombosis of major vessels in foals has been associated with a poor outcome.

Aspirin

The NSAID aspirin has been used for its antipyretic, analgesic, antiinflammatory, and antithrombotic properties for many years. Aspirin inhibits the enzyme cyclooxygenase, thereby reducing the production of prostaglandins and thromboxanes. Platelets are responsible for primary hemostasis by interacting with subendothelial collagen, releasing various mediators, and forming a platelet plug. Thromboxane A_2, a significant product of platelet activation, stimulates vasoconstriction and aggregation of platelets, contributing to platelet plug formation. Inhibition of platelet-derived thromboxane, therefore, thwarts these responses and potentially decreases the propensity for thrombus formation. While most cells can synthesize cyclooxygenase de novo, platelets cannot, once they are inhibited by aspirin. Therefore, aspirin inhibits platelet aggregation for the life of the platelet (3 to 5 days in horses), and establishment of normal platelet function requires production of new platelets.

Aspirin is used infrequently for analgesia in horses because of its relatively short half-life and lower potency compared with other NSAIDs, such as flunixin meglumine and phenylbutazone. However, the antithrombotic effects of aspirin are prolonged; thus intermittent administration of low-dose aspirin (5 to 30 mg/kg PO q24–48h) may help prevent thrombus formation related to DIC, endotoxemia, and thromboembolic diseases such as acute laminitis and vascular occlusion.[3,18,37] While human studies have suggested that aspirin is beneficial for preventing thromboembolic-related disorders, there is a lack of evidence demonstrating the efficacy of aspirin as a prophylactic medication in equine patients pre-

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Thromboxane A_2, a significant product of platelet activation, stimulates vasoconstriction and aggregation of platelets, contributing to platelet plug formation. Inhibition of platelet-derived thromboxane, therefore, thwarts these responses and potentially decreases the propensity for thrombus formation.

disposed to thrombus formation.[38] One equine study suggested that thromboxane A_2 plays a minor role in aggregation of equine platelets and that aspirin is not an effective antithrombotic medication in horses compared with other species.[3,27,39] Controlled equine studies investigating the role of aspirin as an antithrombotic medication in clinical situations are needed.

Warfarin

Warfarin is a coumarin-derivative anticoagulant that has been used to prevent or treat laminitis, thrombophlebitis, and navicular syndrome in horses.[3,40,41] As with other coumarins, the anticoagulant effects of warfarin are indirect via interference with the action of vitamin K_1 in the hepatic synthesis of coagulation factors II, VII, IX, and X. Initial study of warfarin therapy in horses with navicular syndrome proved favorable: 17 of 20 horses became sound after warfarin therapy.[41] A starting dose of 0.018 mg/kg PO q24h was increased by 20% until a 2- to 4-second increase in one-stage prothrombin time was achieved.[41] However, with the advent of newer therapies for navicular syndrome, the adverse effects of warfarin therapy (hemorrhage, hematoma formation, hemarthrosis), and the need for close monitoring of therapy (one-stage prothrombin time), warfarin has been relegated to infrequent use in equine practice.[40,41]

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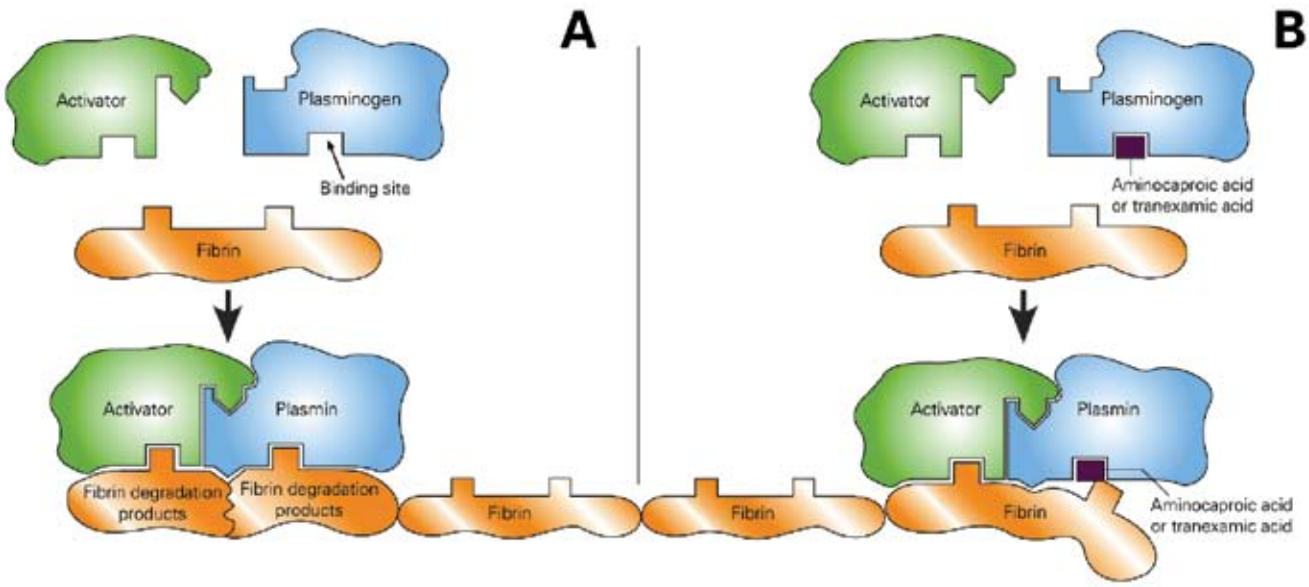
Fibrinolytic medications, such as TPA, urokinase, and streptokinase, dissolve thrombi by promoting the conversion of plasminogen to plasmin.

Fibrinolytic Medications

The fibrinolytic system dissolves intravascular clots via the enzyme plasmin, which digests fibrin and fibrinogen. Plasminogen is the inactive precursor of plasmin, and conversion to the active form results from the interaction of fibrin-bound plasminogen with TPA (**FIGURE 2**). Fibrinolytic medications, such as TPA, urokinase, and streptokinase, dissolve thrombi by promoting the conversion of plasminogen to plasmin. Under normal circumstances, circulating TPA has minimal effect on circulating plasminogen because it is either rapidly cleared from the blood or inhibited by the circulating inhibitors plasminogen activator inhibitor-1 and -2. A distinct disadvantage of thrombolytic medication administration is that

FIGURE 2 **Mechanism of activation and inhibition of plasminogen.**



A **Normal fibrinolysis occurs by binding of plasminogen to fibrin and subsequent activation to plasmin via the interaction with plasminogen activator. Plasmin bound to fibrin results in degradation of fibrin into fibrin degradation products.**

B **Antifibrinolytic medications such as aminocaproic acid and tranexamic acid bind to the site where plasminogen binds to fibrin, thereby preventing activation of plasminogen on the surface of fibrin. Fibrinolysis is therefore blocked. (Adapted with permission.[48])**

natural inhibitors of plasminogen activators may become overwhelmed, resulting in generalized fibrinolysis and hemorrhage.

As noted above, vessel thrombosis can occur during sepsis in neonates as a result of bacteria or endotoxin altering or activating the coagulation cascade. In addition, neonatal foals have a lower protein C concentration and decreased activities of antithrombin and plasminogen during the first month of life, which may contribute to the increased incidence of coagulopathies such as vessel thrombosis in septic foals.[15,42,43] Clinical signs of vessel thrombosis include lameness, cool extremities and tissue edema distal to thrombosis, a lack of a palpable arterial pulse, and sloughing or separation of the skin or hooves. Thrombolytic agents can be administered systemically or regionally (catheter directed); the latter results in better clot resolution in people with peripheral artery thrombi as a result of more direct and localized effects.[44]

The published use of thrombolytic medications is limited in equine medicine. One report detailed the use of a constant-rate infusion of urokinase (4000 U/min for 60 minutes) into the right hindlimb of a 6-day-old Quarter horse filly with thromboembolism of the hindlimbs. Angiography did not show reperfusion of the right hindlimb, and the foal was subsequently euthanized.[45] In another instance, TPA was administered (2 mg IV) in an attempt to dissolve an aortoiliac thrombus in a 5-day-old Quarter horse filly. The foal was subsequently euthanized due to deterioration of its condition and the lack of reperfusion of the hindlimbs.[43] Streptokinase does not activate equine plasminogen, thus limiting its use in horses.[29]

Based on a review of case reports involving vascular thrombosis, a poor prognosis is warranted once arterial thrombosis occurs, as no resolution of vessel thrombosis has been documented and all horses died or were euthanized.[30,32,43,45–47] Poor resolution of thromboembolic disease in horses may be due to the delayed recognition and treatment of thrombosis, inappropriate dosing and frequency of thrombolytic medications, inappropriate delivery methods, and a lack of adjunctive therapies, such as interventional (mechanical thrombectomy) and surgical procedures.

Procoagulant Medications in Treating Severe Hemorrhage

Severe acute hemorrhage from conditions such as trauma, uterine artery rupture, hemothorax, hemoperitoneum, and guttural pouch mycosis occurs occasionally in equine medicine. Adjunctive medications such as formalin, aminocaproic acid, tranexamic acid, and conjugated estrogens have been used to facilitate hemostasis. While these drugs may help promote hemostasis, clinicians should not ignore obvious and potentially lifesaving therapies, such as blood transfusions, fluid therapy with crystalloids and/or colloids, and direct mechanical pressure to control hemorrhage.

> Procoagulant medications (e.g., formalin, aminocaproic and tranexamic acid, conjugated estrogens) may facilitate hemostasis in hemorrhaging horses.

One proposed mechanism by which formalin enhances primary hemostasis is through enhanced endothelial or platelet activation.[48] Ten to 150 mL of 10% buffered formalin diluted in 1 L of isotonic fluid has been suggested to control hemorrhage in horses.[48–50] However, adverse effects such as muscle tremors, tachycardia, tachypnea, serous ocular and nasal discharge, agitation, and restlessness have been observed with doses greater than 4000 mg of formalin (>40 mL of 10% formalin) in experimental studies.[50] These signs abated after discontinuation of administration. Although anecdotal reports have suggested positive results with the use of formalin, one study found no difference in coagulation profiles between healthy horses administered IV formalin and the control group.[49,50] It was suggested that the vasoconstrictive response to hypovolemia along with cytokines and inflammatory mediators present in hemorrhaging horses may enhance the effects of formalin administration. This may explain the lack of response in healthy horses.[50]

Aminocaproic acid and tranexamic acid are synthetic derivatives of lysine that inhibit fibrinolysis primarily by binding and inhibiting plasminogen activation and, to a lesser

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While numerous medications have been used as anticoagulants or antifibrinolytics in horses in various clinical situations, the efficacy of these efforts is largely undefined. Despite this, theoretical benefits of these medications may justify their use until controlled studies can be completed.

TABLE 1 Suggested Medications and Doses for Modifying the Coagulation Cascade in Equine Patients

Medication	Uses/Indications	Suggested Dose	Reference
UFH	Prevention of abdominal adhesions	20–120 U/kg q6–24h systemic or 15,000–50,000 U intraperitoneal	Southwood and Baxter[7]
		40 U/kg IV during surgery, SC immediately after surgery, then q12h for 48 hr after surgery	Parker et al[9]
		80 U/kg SC q12h for 72 hr (foals)	Sullins et al[12]
		66 U/kg SC q12h for 72 hr	Young et al[11]
		30,000–50,000 U in 10 L lavage fluid, intraperitoneal	Eggleston and Mueller[10]
	Prevention or treatment of DIC	40–90 U/kg SC q8h	Welch et al[14]
	Prevention or treatment of hypercoagulable disease or DIC	400 U/L IV of equine plasma	Darien[20]
	Prevention of laminitis associated with proximal enteritis	40–110 U/kg q8–12h systemic	Cohen et al[26]
	Prevention of thrombophlebitis or further extension of existing thrombi	20–40 U/kg SC q12h	Morris[17]
	Prevention of organ thrombosis (secondary to severe infectious colitis)	40 U/kg preincubated with equine plasma, IV	Divers[27]
LMWH	Prophylactic anticoagulant therapy	Dalteparin: 50 U/kg SC q24h	Feige et al[34]
		Enoxaparin: 40 U/kg SC q24h	Schwarzwald et al[35]
	Prophylactic therapy in patients at high risk of thrombotic disease	Dalteparin: 100 U/kg SC q24h Enoxaparin: 80 U/kg SC q24h	Schwarzwald et al[35]
Hirudin	Prophylaxis and treatment of thrombotic disease	0.5–1 mg/kg SC q12h	Feige et al[36]
Aspirin	Prevention or treatment of DIC	15–100 mg/kg PO q8–12h or 30 mg/kg PO q24–48h	Dallap[18]
		20 mg/kg per rectum	Broome et al[a]
		17 mg/kg PO q24–48h	Morris[17]
	Treatment of acute laminitis	5–10 mg/kg PO q24–48h	Brumbaugh et al[3]
		20 mg/kg PO every 4–5 days	Brumbaugh et al[3]
Warfarin	Prevention or treatment of laminitis	0.0198 mg/kg PO q24h Monitor one-step prothrombin time until prolonged 2–4 sec beyond baseline	Brumbaugh et al[3]
	Prevention or treatment of navicular syndrome	0.018 mg/kg PO q24h Increase dose by 20% until 2–4 sec increase in one-step prothrombin time	Colles[41]
Urokinase	Thrombolysis	4000 U/min IV for 60 min	Forrest el al[45]
Tissue plasminogen activator	Thrombolysis	2 mg IV	Duggan et al[43]
Formalin	Control of hemorrhage	10–150 mL of 10% buffered formalin diluted in 1 L of isotonic fluids, IV	Jones,[49] Taylor et al[50]
Aminocaproic acid	Control of hemorrhage	100 mg/kg IV	Heidmann et al[52]
Tranexamic acid	Control of hemorrhage	5 g IV q12h 10 g PO q6h	Dechant[b]
Conjugated estrogens	Control of hemorrhage	3 mg/kg divided over 5 consecutive days, IV or 0.6 mg/kg IV q24h for 5 days (dose used in people)	Livio et al[56]
		25–50 mg IV or IM	Dechant[b]

[a]Broome TA, Brown MP, Gronwall RR, et al. Pharmacokinetics and plasma concentrations of acetylsalicylic acid after intravenous, rectal, and intragastric administration to horses. *Can J Vet Res* 2003;67:297-302.

[b]Personal communication, Dr. Julie Dechant, School of Veterinary Medicine, University of California, Davis (September 2006).

degree, by enhancing α_2-antiplasmin activity[51,52] (**FIGURE 2**). Antifibrinolytic activity is believed to be limited to clot maintenance and stabilization, with no major effect on promoting clot formation through the intrinsic or extrinsic coagulation pathways. In the human literature, there are mixed reviews on the efficacy of aminocaproic acid for minimizing bleeding, but beneficial effects have been demonstrated in controlling intra- or postoperative bleeding and traumatic hyphema.[53,54] No controlled clinical studies have investigated the efficacy of aminocaproic acid and tranexamic acid in hemorrhaging horses. It is unlikely that either medication alone could control blood loss from large vessels in normotensive horses. However, hemorrhage from smaller vessels may be minimized by the administration of aminocaproic or tranexamic acid, particularly when a patient is in a hypotensive state and/or direct mechanical control of bleeding can be instituted.[52] In one study involving healthy horses, aminocaproic acid was administered once at 30 or 100 mg/kg IV; the results demonstrated modest but significantly higher α_2-antiplasmin activity and lower fibrinogen concentrations compared with baseline values at the 100-mg/kg dose.[52] Drug administration was well tolerated, and the effects lasted up to 5 hours after administration. These findings were consistent with the antifibrinolytic effects of aminocaproic acid, and the authors stated that clinical use may benefit some horses.[52] Tranexamic acid is approximately 10 times more potent and has a longer half-life than aminocaproic acid, but it has been used too infrequently in horses with hemoperitoneum to confirm its possible advantages.[51,55]

Bleeding is a common complication in uremic people, but the cause remains unclear.[56] Conjugated estrogens have been used perioperatively and in uremic people to shorten prolonged bleeding times and reduce or stop bleeding, but the exact mechanism of action is unknown. Conjugated estrogens may facilitate hemostasis by reducing capillary and arteriolar permeability through polymerization of mucopolysaccharides in vessel walls and/or by possibly decreasing antithrombin activity.[57] Studies have documented shortened bleeding times in uremic people administered conjugated estrogens, with onset of action noted within 6 hours of administration and a maximum effect between 5 and 7 days (total duration of action: 14 days).[56] The prolonged effects of conjugated estrogens make these agents attractive for situations in which long-lasting hemostasis is required (i.e., reduction of bleeding during elective surgery, recurrent episodes of bleeding).[51] One human study demonstrated decreased need for intraoperative administration of erythrocytes, plasma, and platelets in liver transplant recipients treated with conjugated estrogens at the beginning of surgery compared with the control group.[57] These results suggested a possible benefit of the administration of conjugated estrogens in patients who undergo surgery in which significant blood loss is anticipated. Similar to tranexamic acid, conjugated estrogens have been used to facilitate hemostasis in horses with hemoperitoneum, but the efficacy is unknown.[55]

Conclusion

Many clinical situations in equine practice warrant the use of adjunctive medications to promote or inhibit the coagulation cascade. While numerous medications have been used as anticoagulants or antifibrinolytics in horses in various clinical situations, the efficacy of these efforts is largely undefined. Despite this, theoretical benefits of these medications may justify their use until controlled studies can be completed. **TABLE 1** provides a summary of the drugs, dosages, and indications of the medications discussed in this article.

CriticalPoint

Hemorrhage from smaller vessels may be minimized by the administration of aminocaproic or tranexamic acid, particularly when a patient is in a hypotensive state and/or direct mechanical control of bleeding can be instituted.

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References

1. Weitz JI. Low-molecular-weight heparins. *N Engl J Med* 1997; 337:688-698.

2. Moore BR, Hinchcliff KW. Heparin: a review of its pharmacology and therapeutic use in horses. *J Vet Intern Med* 1994;8:26-35.

3. Brumbaugh G, Lopez H, Sepulveda M. The pharmacologic basis for the treatment of developmental and acute laminitis. *Vet Clin*

North Am Equine Pract 1999;15:345-362.
4. Monreal L, Villatoro AJ, Monreal M, et al. Comparison of the effects of low-molecular-weight and unfractionated heparin in horses. *Am J Vet Res* 1995;56:1281-1285.
5. Byun Y, Singh VK, Yang VC. Low molecular weight protamine: a potential nontoxic heparin antagonist. *Thromb Res* 1999;94:53-61.
6. Chu AJ, Wang ZG, Raicu M, et al. Protamine inhibits tissue factor–initiated extrinsic coagulation. *Br J Haematol* 2001;115:392-399.
7. Southwood LL, Baxter GM. Current concepts in management of abdominal adhesions. *Vet Clin North Am Equine Pract* 1997;13:415-435.
8. Thompson J. Pathogenesis and prevention of adhesion formation. *Dig Surg* 1998;15:153-157.
9. Parker JE, Fibini SL, Car BD, et al. Prevention of intraabdominal adhesions in ponies by low-dose heparin therapy. *Vet Surg* 1987;16:459-462.
10. Eggleston RB, Mueller PO. Prevention and treatment of gastrointestinal adhesions. *Vet Clin North Am Equine Pract* 2003;19:741-763.
11. Young DR, Richardson DW, Markel MD. The effect of low dose heparin therapy on complication and survival rates in horses following exploratory celiotomy. *Equine Vet J Suppl* 1989;(7):91-93.
12. Sullins KE, White NA, Lundin CS, et al. Prevention of ischaemia-induced small intestinal adhesions in foals. *Equine Vet J* 2004;36:370-375.
13. Levi M, Ten Cate H. Disseminated intravascular coagulation. *N Engl J Med* 1999;341:586-592.
14. Welch RD, Watkins JP, Taylor TS, et al. Disseminated intravascular coagulation associated with colic in 23 horses (1984-1989). *J Vet Intern Med* 1992;6:29-35.
15. Barton MH, Morris DD, Norton N, et al. Hemostatic and fibrinolytic indices in neonatal foals with presumed septicemia. *J Vet Intern Med* 1998;12:26-35.
16. Dolente BA, Wilkins PA, Boston RC. Clinicopathologic evidence of disseminated intravascular coagulation in horses with acute colitis. *JAVMA* 2002;220:1034-1038.
17. Morris DD. Recognition and management of disseminated intravascular coagulation in horses. *Vet Clin North Am Equine Pract* 1988;4:115-143.
18. Dallap BL. Coagulopathy in the equine critical care patient. *Vet Clin North Am Equine Pract* 2004;20:231-251.
19. Zhang Y, Scandura JM, Van Nostrand WE, et al. The mechanism by which heparin promotes the inhibition of coagulation factor XIa by protease nexin-2. *J Biol Chem* 1997;272:26139-26144.
20. Darien BJ. Heparin therapy: rationale and clinical indications. *Compend Contin Educ Pract Vet* 1993;15:1273-1276.
21. Kienast J, Juers M, Wiedermann CJ, et al. Treatment effects of high-dose antithrombin without concomitant heparin in patients with severe sepsis with or without disseminated intravascular coagulation. *J Thromb Haemost* 2006;4:90-97.
22. Iba T, Kidokoro A, Fukunaga M, et al. Antithrombin ameliorates endotoxin-induced organ dysfunction more efficiently when combined with danaparoid sodium than with unfractionated heparin. *Intensive Care Med* 2005;31:1101-1108.
23. Weiss DJ, Evanson OA, McClenahan D, et al. Effect of a competitive inhibitor of platelet aggregation on experimentally induced laminitis in ponies. *Am J Vet Res* 1998;59:814-817.
24. Stashak T. The foot. In: Stashak T, ed. *Adam's Lameness in Horses.* 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2002:645-664.
25. Belknap JK, Moore JN. Evaluation of heparin for prophylaxis of equine laminitis: 71 cases (1980-1986). *JAVMA* 1989;195:505-507.
26. Cohen ND, Parson EM, Seahorn TL, et al. Prevalence and factors associated with development of laminitis in horses with duodenitis/proximal jejunitis: 33 cases (1985-1991). *JAVMA* 1994;204:250-254.
27. Divers TJ. Prevention and treatment of thrombosis, phlebitis, and laminitis in horses with gastrointestinal diseases. *Vet Clin North Am Equine Pract* 2003;19:779-790.
28. Morris DD, Beech J. Disseminated intravascular coagulation in six horses. *JAVMA* 1983;183:1067-1072.
29. Morris D. Thrombophlebitis in horses: the contribution of hemostatic dysfunction to pathogenesis. *Compend Contin Educ Pract Vet* 1989;11:1386-1395.
30. Brianceau P, Divers TJ. Acute thrombosis of limb arteries in horses with sepsis: five cases (1988-1998). *Equine Vet J* 2001;33:105-109.
31. Carr EA, Carlson GP, Wilson WD, et al. Acute hemorrhagic pulmonary infarction and necrotizing pneumonia in horses: 21 cases (1967-1993). *JAVMA* 1997;210:1774-1778.
32. Triplett EA, O'Brien RT, Wilson DG, et al. Thrombosis of the brachial artery in a foal. *J Vet Intern Med* 1996;10:330-332.
33. Davidson BL. Risk assessment and prophylaxis of venous thromboembolism in acutely and/or critically ill patients. *Haemostasis* 2000;30(suppl 2):77-81.
34. Feige K, Schwarzwald CC, Bombeli T. Comparison of unfractioned and low molecular weight heparin for prophylaxis of coagulopathies in 52 horses with colic: a randomised double-blind clinical trial. *Equine Vet J* 2003;35:506-513.
35. Schwarzwald CC, Feige K, Wunderli-Allenspach H, et al. Comparison of pharmacokinetic variables for two low-molecular-weight heparins after subcutaneous administration of a single dose to horses. *Am J Vet Res* 2002;63:868-873.
36. Feige K, Dennler M, Kastner SB, et al. Pharmacokinetics of recombinant hirudin in healthy horses. *Equine Vet J* 2004;36:135-141.
37. Cambridge H, Lees P, Hooke RE, et al. Antithrombotic actions of aspirin in the horse. *Equine Vet J* 1991;23:123-127.
38. Hovens MM, Snoep JD, Tamsma JT, et al. Aspirin in the prevention and treatment of venous thromboembolism. *J Thromb Haemost* 2006;4:1470-1475.
39. Heath MF, Evans RJ, Poole AW, et al. The effects of aspirin and paracetamol on the aggregation of equine blood platelets. *J Vet Pharmacol Ther* 1994;17:374-378.
40. Scott EA, Byars TD, Lamar AM. Warfarin anticoagulation in the horse. *JAVMA* 1980;177:1146-1151.
41. Colles CM. A preliminary report on the use of warfarin in the treatment of navicular disease. *Equine Vet J* 1979;11:187-190.
42. Barton MH, Morris DD, Crowe N, et al. Hemostatic indices in healthy foals from birth to one month of age. *J Vet Diagn Invest* 1995;7:380-385.
43. Duggan VE, Holbrook TC, Dechant JE, et al. Diagnosis of aorto-iliac thrombosis in a Quarter horse foal using Doppler ultrasound and nuclear scintigraphy. *J Vet Intern Med* 2004;18:753-756.
44. Razavi MK, Lee DS, Hofmann LV. Catheter-directed thrombolytic therapy for limb ischemia: current status and controversies. *J Vasc Interv Radiol* 2003;14:1491-1501.
45. Forrest LJ, Cooley AJ, Darien BJ. Digital arterial thrombosis in a septicemic foal. *J Vet Intern Med* 1999;13:382-385.
46. Moore LA, Johnson PJ, Bailey KL. Aorto-iliac thrombosis in a foal. *Vet Rec* 1998;142:459-462.
47. Spier S. Arterial thrombosis as the cause of lameness in a foal. *JAVMA* 1985;187:164-165.
48. Doyle AJ, Freeman DE, Rapp H, et al. Life-threatening hemorrhage from enterotomies and anastomoses in 7 horses. *Vet Surg* 2003;32:553-558.
49. Jones W. IV formalin to control hemorrhage. *J Equine Vet Sci* 1998;18:581.
50. Taylor EL, Sellon DC, Wardrop KJ, et al. Effects of intravenous administration of formaldehyde on platelet and coagulation variables in healthy horses. *Am J Vet Res* 2000;61:1191-1196.
51. Mannucci PM. Hemostatic drugs. *N Engl J Med* 1998;339:245-253.
52. Heidmann P, Tornquist SJ, Qu A, et al. Laboratory measures of hemostasis and fibrinolysis after intravenous administration of epsilon-aminocaproic acid in clinically normal horses and ponies. *Am J Vet Res* 2005;66:313-318.
53. Pieramici DJ, Goldberg MF, Melia M, et al. A phase III, multicenter, randomized, placebo-controlled clinical trial of topical aminocaproic acid (Caprogel) in the management of traumatic hyphema. *Ophthalmology* 2003;110:2106-2112.
54. Tobias JD. Strategies for minimizing blood loss in orthopedic surgery. *Semin Hematol* 2004;41:145-156.
55. Dechant JE, Nieto JE, Le Jeune SS. Hemoperitoneum in horses: 67 cases (1989-2004). *JAVMA* 2006;229:253-258.
56. Livio M, Mannucci PM, Vigano G, et al. Conjugated estrogens for the management of bleeding associated with renal failure. *N Engl J Med* 1986;315:731-735.
57. Erstad BL. Systemic hemostatic medications for reducing surgical blood loss. *Ann Pharmacother* 2001;35:925-934.

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1. The primary mechanism of action of heparin is
- **a.** to block interaction of plasminogen with TPA.
- **b.** inactivation of thrombin and factor Xa.
- **c.** inactivation of factor VII.
- **d.** suppression of antithrombin.

2. A common adverse effect of heparin administration in horses is
- **a.** leukopenia.
- **b.** leukocytosis.
- **c.** hypofibrinogenemia.
- **d.** anemia.

3. LMWH combines with antithrombin; together, the complex has the greatest affinity to bind to
- **a.** factor VIa.
- **b.** thrombin.
- **c.** factor Xa.
- **d.** factor XII.

4. The anticoagulant activity of hirudin results from direct inhibition of
- **a.** factor X.
- **b.** plasminogen.
- **c.** antithrombin.
- **d.** thrombin.

5. Aspirin
- **a.** inhibits cyclooxygenase and lipoxygenase.
- **b.** has profound analgesic properties at low doses.
- **c.** inhibits platelet aggregation.
- **d.** has a long half-life in horses.

6. Which coagulation factor is not blocked by the actions of warfarin?
- **a.** VI
- **b.** VII
- **c.** IX
- **d.** X

7. Fibrinolytic medications such as urokinase promote clot resolution by facilitating conversion of
- **a.** prothrombin to thrombin.
- **b.** fibrinogen to fibrin.
- **c.** plasminogen to plasmin.
- **d.** antithrombin to thrombin.

8. Which adverse effect is not associated with the administration of formalin?
- **a.** tachycardia
- **b.** serous ocular and nasal discharge
- **c.** muscle tremors
- **d.** petechiae

9. Aminocaproic acid and tranexamic acid inhibit fibrinolysis by
- **a.** inhibiting plasminogen activation.
- **b.** inhibiting α_2-antiplasmin activity.
- **c.** promoting plasminogen activation.
- **d.** promoting thrombin formation.

10. The procoagulant activity of conjugated estrogens arises from
- **a.** inhibition of TPA activity.
- **b.** blockage of fibrin from the plasminogen binding site.
- **c.** inhibition of antithrombin activity.
- **d.** none of the above; the exact mechanism is unknown.