



PRACTICAL PHARMACOLOGY

Antifibrinolytic Drugs in Small Animal Medicine

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Normal hemostasis is balance between prothrombotic (clotting) and antithrombotic (bleeding) tendencies. An antithrombotic tendency is necessary for blood to remain in a fluid state for effective circulation. This is achieved through several processes that limit clot formation and persistence, including activation of fibrinolysis. In the event of blood vessel injury, coagulation is actually activated in conjunction with fibrinolysis. This allows thrombosis to be restricted to the site of vessel injury alone and eventually restore blood vessel patency once blood vessel repair has occurred. Normal fibrinolysis is primarily mediated by plasmin and is initiated by binding of its precursor,

plasminogen, to lysine residues on fibrin clots. Once clot bound, plasminogen is converted to plasmin under the influence of tissue plasminogen activator (tPA), with the clot degraded to fibrin degradation products (FDPs). D-dimers are an important subset of FDPs that represent cross-linked subfractions of fibrin that were previously contained with blood clots. The fibrinolytic system is kept in check via 3 mechanisms: plasminogen activator inhibitor-1 (PAI-1), which inhibits tPA; α_2 -antiplasmin, which inhibits plasmin directly; and thrombin-activatable fibrinolysis inhibitor (TAFI), which removes lysine residues from blood clots.¹

Abstract

Fibrinolysis refers to plasmin-mediated clot breakdown, which can be exaggerated in certain disease states, leading to severe bleeding. Antifibrinolytic drugs, including tranexamic acid and epsilon-aminocaproic acid, are a useful addition to the toolbox for the treatment of bleeding in small animals. These drugs are lysine analogs, which prevent binding of plasminogen to fibrin-binding sites on blood clots, limiting the conversion of plasminogen to plasmin and therefore preventing clot degradation. Common situations to consider antifibrinolytic drugs include in traumatic and surgical hemorrhage (e.g., spontaneous hemoperitoneum), in perioperative bleeding in certain breeds of dog (e.g., greyhounds), or as an adjunctive hemostatic agent in coagulopathies (e.g., hemophilia A). These drugs are well tolerated in most dogs, although patient selection is important to avoid development of inadvertent issues (e.g., obstructive blood clot in cases of urinary tract bleeding). Less information about the use of antifibrinolytic drugs in cats is available, although these drugs might play a role similar to their use in dogs.



Take-Home Points

- Antifibrinolytic drugs, specifically tranexamic acid and epsilon-aminocaproic acid, are indicated to support hemostasis by inhibiting fibrinolysis and therefore supporting clot persistence.
- Potential situations where antifibrinolytic drugs might be considered include in severe traumatic bleeding, in perioperative bleeding in greyhounds, as an adjunct to the management of coagulopathies (e.g., hemophilia A), and for the palliative treatment of neoplastic bleeding (e.g., right atrial masses).
- Few contraindications or safety issues exist in dogs. Tranexamic acid is a potent emetic agent; therefore, premedication with maropitant is recommended. Antifibrinolytic drugs should be avoided in cases of suspected disseminated intravascular coagulation.

DISORDERED FIBRINOLYSIS

Reduced fibrinolytic activity (hypofibrinolysis) in dogs could contribute to a prothrombotic state but is less well understood than exaggerated fibrinolysis (hyperfibrinolysis).¹ Hyperfibrinolysis is recognized as an important cause of hemorrhage in humans that has the potential to be severe and clinically relevant (e.g., impacting survival, requiring transfusion administration).² Acquired hyperfibrinolysis associated with clinically relevant bleeding has also been described in several situations in dogs, including severe trauma, spontaneous hemoperitoneum, acute liver disease, and lungworm (*Angiostrongylus vasorum*) infections. Hyperfibrinolysis has also been suggested as an explanation for the increased bleeding tendency noted in greyhounds.³

Laboratory tests can be used to assess fibrinolytic activity in individual patients, although their availability varies from hospital to hospital. The most readily available test is the D-dimer test, offered by many reference laboratories. In some hospitals, viscoelastic testing (e.g., thromboelastography, VCM Vet [Entegriion, vcmmvet.com]) might also be available and provides patient-side insight into clot persistence. In clinical situations, however, it is not necessary to confirm hyperfibrinolysis with lab tests. Patients with bleeding that fit the clinical scenarios mentioned above (e.g., perioperative bleeding in a greyhound) raise an index of suspicion for hyperfibrinolysis being present.

CLINICAL MANAGEMENT OF HYPERFIBRINOLYSIS

Antifibrinolytic drugs are an option for patients with bleeding where hyperfibrinolysis is confirmed or reasonably suspected. Lysine analog drugs, specifically tranexamic acid (TXA) and epsilon-aminocaproic acid

(EACA), are the primary drug option for this purpose. These drugs interact with lysine binding sites on plasminogen that reversibly prevents its binding to the fibrin clot. In effect, these drugs block the step required for plasminogen binding and therefore subsequently prevent plasmin-mediated degradation of the blood clot.

Both TXA and EACA can be used successfully in dogs, provided an appropriate dose is used, as TXA is approximately 8 to 10 times more potent than EACA. Dogs are known to be relatively hyperfibrinolytic compared to humans, meaning higher doses of these drugs are necessary to inhibit fibrinolysis in dogs.⁴ A range of doses are used clinically for these drug classes. TXA is often administered as an IV bolus followed by a constant-rate infusion, with an initial dose of 10 mg/kg IV followed by 10 mg/kg/h infusion over 3 hours being safe in healthy dogs.⁵ For EACA, doses of 50 to 100 mg/kg IV q6h are common, with 100 mg/kg being more effective at inhibiting fibrinolysis compared to 20 mg/kg doses.⁶ The timing of administration appears to be important based on human trauma patient data, which showed a reduction in mortality when administered early (<3 hours).^{7,8} In greyhounds, it is reasonable to consider preemptive administration of antifibrinolytic drugs before the onset of surgery (e.g., 1 hour before).

Antifibrinolytic drugs tend to be used in hospitalized dogs as a means of achieving hemostasis.⁹ Administration of EACA significantly decreased the incidence of bleeding in greyhounds undergoing limb amputation and gonadectomy.^{9,10} In this context, administration of antifibrinolytic drugs has potential benefits (e.g., reduced requirement for transfusion), although this has not been clearly demonstrated in dogs.⁹⁻¹² Antifibrinolytic drugs might also be considered

as an adjunct to conventional therapy for other bleeding disorders (e.g., factor VIII deficiency in hemophilia A). Recently, however, a study described that EACA did not impact outcome for dogs with severe thrombocytopenia (e.g., immune-mediated thrombocytopenia) with respect to transfusion administration or duration of hospitalization.¹³

The optimal duration of antifibrinolytic drug administration is less well understood. For example, the hyperfibrinolytic tendency noted in dogs with spontaneous hemoperitoneum rapidly corrected after surgical hemostasis was obtained, suggesting that short-term administration is appropriate in this context.¹⁴ Likewise, the hypocoagulable and hyperfibrinolytic tendency noted in severe trauma in humans is known to “flip” to a hypercoagulable and antifibrinolytic tendency over time. In practice, the author typically uses antifibrinolytic drugs for a 12- to 24-hour period only, although administration for 3 days has been described in greyhounds.¹² There are some patient populations, however, for which longer-term antifibrinolytic administration could be considered (e.g., as a palliative care measure in dogs with right atrial masses due to hemangiosarcoma).

One study compared the outcome for dogs managed with EACA and Yunnan Baiyao versus Yunnan Baiyao alone. Yunnan Baiyao is a Chinese herb that has gained popularity in small animal practice recently as a hemostatic agent, although there is limited information to support its efficacy and it has not been assessed by the U.S. Food and Drug Administration. Dogs with right atrial masses tolerated both interventions well, but neither intervention significantly delayed recurrence of clinical signs or improved outcome in affected patients.¹⁵

Pragmatically, antifibrinolytic drugs can be considered in cats for similar reasons considered in dogs and humans, although there is less clinical experience with these drugs in cats overall.

The oral bioavailability of EACA is good in dogs, and the injectable version of the drug can be administered intraorally as a reasonable “at-home” option.⁶

ADVERSE EFFECTS AND CONTRAINDICATIONS OF ANTIFIBRINOLYTIC DRUGS

Antifibrinolytic drugs appear to be well tolerated in dogs and humans, with thromboembolic complications being rarely reported in people. It is prudent to consider if the development of blood clots could lead to unexpected complications. In the author’s experience, blood clots in the urinary bladder can develop after administration of antifibrinolytic drugs in cases of urinary tract hemorrhage that could obstruct normal urinary flow. Antifibrinolytic drugs are also controversial in cases of disseminated intravascular coagulation (DIC).

In DIC, a precipitating event activates coagulation, leading to widespread thrombin generation and subsequent clot formation. In response, hyperfibrinolysis associated with DIC is triggered and explains the elevated D-dimers noted in affected patients. Antifibrinolytic administration is avoided in this situation for fear of supporting persistence of these blood clots that worsens the consumptive coagulopathy underpinning clinically relevant bleeding.

Another consideration for TXA specifically is its tendency to result in vomiting in dogs, to the extent that it has been described as an emesis induction agent.¹⁶ Premedication with maropitant circumvents the risk of vomiting in dogs.¹⁷ Lastly, dose reduction of TXA and EACA is recommended in humans with kidney insufficiency, although specific advice in dogs has not been established.¹⁸

ANTIFIBRINOLYTIC DRUGS IN CATS

Recently, a retrospective multicenter study outlined the use of TXA in 30 cats and EACA in 5 cats.¹⁹

Antifibrinolytic drugs were used for cats with bleeding (54% nontraumatic and 17% traumatic) and in the perioperative period (11%). This study identified complications in about 20% of cats, although several of these complications could be explained by their illness severity. Older references described neurologic and respiratory complications in cats administered TXA at high doses for prolonged periods. The likelihood of these complications occurring appears less likely at the



doses typically used in cats. Pragmatically, antifibrinolytic drugs can be considered in cats for similar reasons as in dogs and humans, although there is less clinical experience with these drugs in cats overall.

SUMMARY

Antifibrinolytic drugs, specifically TXA and EACA, are a helpful addition to the toolbox for the treatment of bleeding in small animals. While it is possible to confirm hyperfibrinolytic tendency with lab tests, it is reasonable to consider the use of these drugs in clinical situations where bleeding has been associated with hyperfibrinolysis. In practice, this usually encompasses traumatic and surgical bleeding and the perioperative management of greyhounds. Antifibrinolytic drugs are generally well tolerated, should be administered as early as possible, and are typically needed for short periods only (<24 hours). Premedication with an antiemetic is advisable prior to antifibrinolytic drug administration, specifically for TXA. **TVP**

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Disclosure

Dr. Lynch has worked with Entegron, the manufacturer of VCM Vet.



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