Thrombolytic Therapy in Dogs and Cats

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Abstract

Objective: To review the thrombolytic agents most commonly used in humans, their mechanisms of action, potential uses, adverse effects, and reports of their use in dogs and cats.

Human data synthesis: Thrombolytic agents available in human medicine include streptokinase, urokinase, tissue-plasminogen activator (t-PA), single-chain urokinase plasma activator (scu-PA) and anisoylated plasminogen-streptokinase activator complex (APSAC). These agents were originally used for the management of proximal deep vein thrombosis and severe pulmonary embolism but more recently, use of these drugs has been extended to include the treatment of acute peripheral arterial disease, cerebrovascular disease (stroke) and acute coronary thrombosis. The most predictable side effect associated with the use of thrombolytic therapy is hemorrhage.

Veterinary data synthesis: Clinical experience with thrombolytic agents in small animals is limited to streptokinase and t-PA. It is possible, that as in humans, canine and feline patients with PTE and right ventricular dysfunction may benefit from thrombolytic therapy but there are no veterinary studies to support this theory to date. Successful use of streptokinase has been documented in a small number of canine patients with systemic thromboembolism.[63] Thrombolytic therapy is relatively efficacious in cats with aortic thromboemboli but is associated with a high mortality rate.[59,60,64] With regard to use of t-PA in veterinary medicine, the small number of animals treated with varying protocols makes it impossible to provide safe and effective dose recommendations at this time.

Conclusions: Future goals for thrombolytic therapy in veterinary medicine include determination of more specific clinical indications, as well as design of effective protocols that minimize mortality and morbidity. *(J Vet Emerg Crit Care 2001; 11(2): 111-121)*

Key words

thrombosis, thromboembolism, thrombolysis, fibrinolysis, hypercoagulable

Introduction

Thrombolytic agents are drugs that lyse thrombi and thromboemboli within blood vessels. The goal of thrombolytic therapy is to restore circulation through a previously occluded vessel, and to accomplish this rapidly enough so that the procedure is clinically beneficial, and the risks of therapy justifiable.

In human medicine, thrombolytic agents were originally used for the management of proximal deep vein thrombosis and severe pulmonary embolism. More recently, the use of these drugs has been extended to include treatment of acute peripheral arterial occlusive disease, cerebrovascular disease (stroke) and acute coronary thrombosis.[1,2] Currently, the most frequent indication for thrombolytic therapy in humans is acute myocardial infarction (MI), where reduced mortality has been documented via several large controlled clinical trials.[3-6]

Experience with the use of thrombolytic agents in veterinary medicine is extremely limited. Thromboembolic disease appears to be less common in small animal patients than it is in humans. Inherited hypercoagulable states such as congenital antithrombin III deficiency, have not been documented in dogs and cats. Atherosclerosis, the primary underlying cause of myocardial infarction and peripheral vascular disease in humans, is rarely reported, while deep vein thrombosis is not recognized as a risk factor for pulmonary thromboembolism (PTE) in animals as it is in humans. In addition, there is a limited ability to diagnose such disorders in small animals. This is particularly true for pulmonary thromboembolism, for which the clinical signs and diagnostic findings may be very non-specific.[7,8] Finally, the high cost of thrombolytic agents and lack of established protocols for their administration and monitoring have hampered use of these agents.

Pulmonary and systemic thromboembolism, however, are recognized as potentially devastating complications in veterinary patients, and may represent indications for thrombolytic therapy. This article reviews natural thrombolysis and the mechanism of action, potential uses, and

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adverse effects of thrombolytic agents in dogs and cats. Parallel uses of thrombolytic agents in human medicine are highlighted.

Natural Thrombolysis

The process of thrombolysis (fibrinolysis) is responsible for dissolution of small fibrin thrombi that form following injury and is important in maintaining the patency of blood vessels.[9] Decreased fibrinolytic activity has been documented or implicated in many hypercoagulable states in humans.[10] All of the currently available thrombolytic agents act by accelerating natural thrombolysis.

Thrombolysis begins when the injured tissues and vascular endothelium respond to thrombus formation with slow release of tissue plasminogen activator (t-PA) which converts the inactive proenzyme, plasminogen, into the fully active serine protease plasmin (Figure 1).[9] This requires the enzymatic cleavage of a single peptide bond in the plasminogen molecule.[11] Plasmin is a proteolytic enzyme resembling pancreatic trypsin, that catalyzes fibrin breakdown.[9]

Tissue plasminogen activator normally exists in low concentrations in the plasma, and secretion is controlled by physical and hormonal factors such as venous pressure and vasoactive substances including thrombin.[12] Thrombin concurrently stimulates the release of an endogenous inhibitor of t-PA, plasminogen activator inhibitor 1 (PAI-1), from the endothelium and platelets. Tissue plasminogen activator and PAI-1 bind to each other and circulate in plasma until the resultant complex is adsorbed onto the fibrin meshwork. Plasminogen activator inhibitor is then released back into the circulation, and the t-PA transforms the thrombus-bound plasminogen to plasmin. The enzymatic activity of t-PA is greatly enhanced by transformation of fibrin to fibrin polymer, possibly because this induces a conformational change in either t-PA or plasminogen.[13]
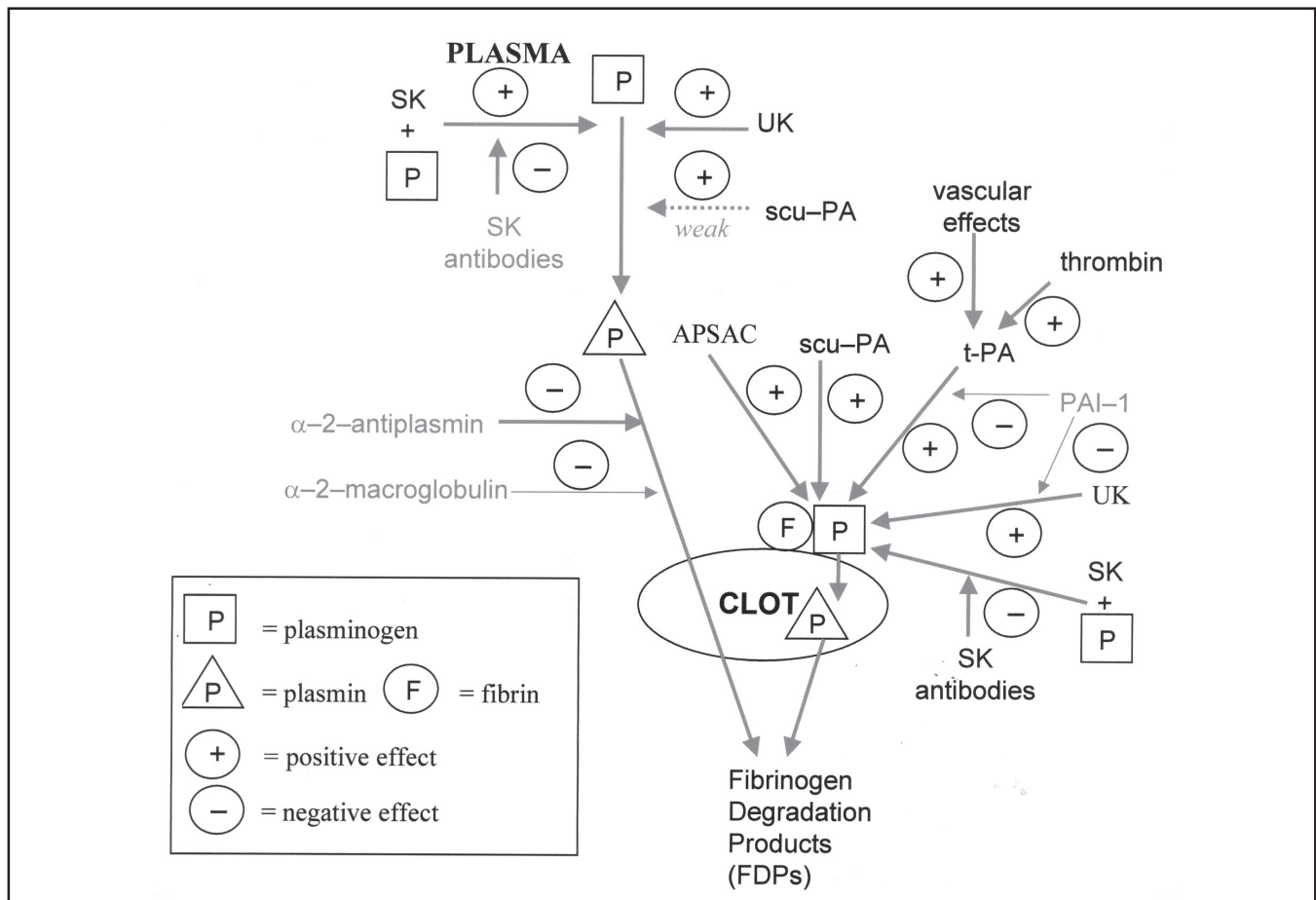

FIGURE 1: Outline of fibrinolysis and the sites of action of the major thrombolytic agents where SK= streptokinase, UK= urokinase, t-PA= tissue plasminogen activator, scu-PA= single chain urokinase plasminogen activator, APSAC= anisoylated plasminogen streptokinase activator complex and PAI-1= plasminogen activator inhibitor-1. Fibrin-specific agents activate plasminogen at the clot surface and non-specific agents activate both clot-associated and plasma plasminogen. Plasmin catalyzes the conversion of fibrin to fibrin degradation products (FDP). Circulating inhibitors of plasmin include α-2- antiplasmin and α-2- macroglobulin. Streptokinase can be inactivated by anti-streptokinase antibodies and t-PA and urokinase by plasminogen activator inhibitor 1 (PAI-1).

Single chain urokinase plasminogen activator (scu-PA) also exists in the plasma at a very low concentration and participates in natural thrombolysis.[14] Cleavage of a peptide bond in scu-PA facilitates conversion to a two-chain derivative, urokinase, which exists in high molecular (HMW) and low molecular weight (LMW) forms. Urokinase activates plasminogen in a direct catalytic reaction and can also be inactivated by PAI-1.[14,15]

Plasmin is formed in the blood on a continuous basis but is rapidly bound and inactivated by circulating proteases, moderating the effect of plasmin on the function of the clotting system.[16,17] The major circulating inhibitor of plasmin is α-2-antiplasmin or α-plasmin inhibitor, with α-2-macroglobulin contributing to this inhibition (Figure 1).[16,18]

Thrombolytic Agents

All of the thrombolytic agents currently in use or under development act directly or indirectly as plasminogen activators, converting inactive plasminogen to active plasmin. These can be grouped into three major categories:

(a) **First generation:** This group includes streptokinase (SK) and urokinase (UK) which are naturally-occurring thrombolytic agents. First generation activators generally lack fibrin specificity, which theoretically increases the risk of a secondary hypocoagulable state attributable to non-specific degradation of fibrinogen, factors V, VII, XII, and prothrombin.[15]

(b) **Second generation:** These are endogenous agents that possess some fibrin selectivity. Second generation activators, which include tissue plasminogen activator (t-PA) and single chain urokinase plasminogen activator (scu-PA or pro-UK) can be produced either as products from selected human cell cultures or by recombinant DNA methods.[19]

(c) **Third generation:** This group includes anisoylated plasminogen-streptokinase activator complex (APSAC) and numerous compounds in early development. These proteins possess enhanced properties as a result of chemical modification or recombinant DNA technology which increases and prolongs fibrin specificity activity.[1]

• Streptokinase

Streptokinase (SK) was one of the first thrombolytic agents developed and is still the most widely used agent in human medicine. Streptokinase has been used in humans for the treatment of myocardial infarction, pulmonary embolism, proximal deep vein thrombosis, acute peripheral artery thrombosis, and for recanalization of indwelling catheters and arteriovenous shunts.[1]

Streptokinase does not directly convert plasminogen to plasmin and, therefore, is not considered an enzyme in the classical sense.[19] It acts by binding to plasminogen in a 1:1 ratio, forming an active enzymatic complex capable of subsequent conversion of other plasminogen molecules to plasmin.[1,11] Streptokinase is produced by beta-hemolytic streptococci and is potentially antigenic. Streptokinase does not possess any direct fibrin binding properties, activating both thrombus-associated and free-plasminogen. In addition to the thrombolytic activity, streptokinase causes rapid degradation of the circulating fibrinogen pool and subsequent accumulation of fibrinogen degradation products.[1] These degradation products may then interrupt newly forming fibrin networks by substituting for fibrinogen in the process of fibrin polymerization. Coagulation factors including V, VIII, and prothrombin are also degraded, giving streptokinase the potential to cause a massive coagulation defect.[1,19] Although the half-life of streptokinase is approximately 30 minutes, depletion of fibrinogen may continue for 24 hours.[20]

• Urokinase

Urokinase (UK) is found in urine and can be produced using human fetal kidney cells in tissue culture.[19] Commercial preparations of urokinase predominantly consist of HMW urokinase and minor proportions of LMW urokinase, but the two forms are equipotent plasminogen activators. High molecular weight urokinase is continually converted into LMW urokinase in the bloodstream.[15]

In contrast to streptokinase, the action of urokinase is relatively fibrin-specific.[15,19] Fibrin specificity is attributed to the binding characteristics of LMW and HMW urokinase for plasminogen. Plasminogen exists in two forms, glutamate-plasminogen (GLU-plasminogen) and lysine-plasminogen (LYS-plasminogen). Lysine-plasminogen accumulates within the thrombus and LMW urokinase has greater affinity for this form of plasminogen, giving it increased fibrin specificity.[15] During thrombolytic therapy, continuous conversion of GLU- to LYS-plasminogen occurs such that LYS-plasminogen, and subsequently, urokinase bind to new lysine binding sites on the fibrin clot as they are unveiled. The half-life of urokinase is approximately 16 minutes in humans, and thrombolytic activity ceases rapidly following cessation of infusion.[19] An important advantage of urokinase over streptokinase in humans is the lack of antigenicity.[1] This, however, cannot be assumed in the dog and cat.

Urokinase has been used in human medicine in the treatment of almost all indications for which streptokinase has also been utilized. Limited data has been collected in randomized clinical trials and definite recommendations have only been issued for acute myocardial infarction and pulmonary embolism.[21-23]

• Tissue Plasminogen Activator

Recombinant tissue plasminogen activator (t-PA) is a single-chain polypeptide serine protease that was originally synthesized from c-DNA obtained from a human melanoma cell line. Tissue plasminogen activator can now

be produced in different cell types including mammalian cells, E. coli, and yeast.[15,24] The product is non-antigenic in humans, but the antigenicity in dogs and cats has not been investigated. The mechanism of action of t-PA involves formation of a complex between fibrin, t-PA, and plasminogen.[15] Tissue plasminogen activator has a high affinity for fibrin due to a fibrin binding site, preferentially activating thrombus-associated plasminogen.[25] While t-PA is a weak activator of plasminogen in the absence of fibrin, the presence of fibrin produces a 500 to 1000 fold increase in activation.[19] Although the fibrin specificity of t-PA increases the likelihood of effective thrombolysis without production of systemic plasma proteolysis, the benefits of this specificity are limited. Importantly, the fibrin specificity of t-PA is relative, and when the dose of t-PA is increased to achieve effective thrombolysis, the risk of plasma proteolysis and excessive bleeding increases.[15,25] Tissue plasminogen activator has a half-life of 2 to 3 minutes, but prolonged fibrinolytic activity may occur due to enhanced binding of t-PA to fibrin, providing protection of both fibrin-bound t-PA and plasmin from their inhibitors.[17,26]

It has been suggested that bolus dosing of t-PA may be used to achieve a higher concentration of drug over a shorter period of time, potentially maximizing clot lysis while decreasing risk of bleeding.[27] In two prospective, randomized trials in humans with pulmonary thromboembolism, however, bolus dosing of t-PA was not safer or more effective than a 2-hour infusion.[28,29]

In human clinical practice, t-PA is predominantly used for thrombolysis in cases of acute myocardial infarction and acute pulmonary embolism.[15] In comparison to streptokinase, t-PA is less antigenic, does not induce hypotension, and is the preferred treatment for lysis of aged thrombi.[30,31] Acute reperfusion rates have been demonstrated to be higher with t-PA, however, by 24 hours no difference in patency has been demonstrated between t-PA and either streptokinase or urokinase.[9,15,30,32,33]

• Single Chain Urokinase-type Plasminogen Activator

Single chain urokinase-type plasminogen activator (scu-PA or pro-UK) is a second generation plasminogen activator produced by recombinant technologies in mammalian cells or in E. coli.[19] Plasma inhibitors of scu-PA have not been demonstrated.[34,35] Although scu-PA does not bind directly to fibrin, it activates thrombus-associated LYS-plasminogen much more readily than the unbound GLU-plasminogen present in plasma. Species variability in fibrinolytic responses to scu-PA has been reported.[34] Single-chain urokinase-type plasminogen activator is rapidly metabolized in the liver with a half-life of 7 to 8 minutes in humans, but like t-PA, has been shown to have a longer than expected thrombolytic effect.[36,37]

Single-chain urokinase-type plasminogen activator has been shown to have comparable coronary patency rates compared with t-PA or streptokinase in myocardial infarction.[38-41]

• Anisoylated Plasminogen-streptokinase Activator Complex

Anisoylated plasminogen-streptokinase activator complex (APSAC) is a third generation plasminogen activator derived from a chemical modification of streptokinase that has increased fibrin specificity and a prolonged half-life in plasma.[19,30] The plasminogen-streptokinase complex is formed in vitro, with acylation of an essential serine in the catalytic site of plasminogen. Anisoylated plasminogen-streptokinase activator complex does not possess enzymatic activity but the plasminogen component is capable of binding to fibrin. Once bound to fibrin, deacylation occurs and allows the complex to activate other plasminogen molecules without creating the systemic fibrinogenolysis characteristic of streptokinase.[38-40] An additional advantage of APSAC over streptokinase is that the acyl group blocks the binding of anti-streptococcal antibodies, thereby eliminating its inactivation in plasma by these circulating inhibitors.[38]

Anisoylated plasminogen-streptokinase activator complex is significantly more fibrin specific than either urokinase or streptokinase but less so than t-PA.[30] In trials of APSAC in rabbits and guinea pigs, the compound had higher thrombolytic activity than an equal amount of non-acylated streptokinase complex and did not cause systemic fibrinogenolysis.[23] Studies in humans have shown that higher perfusion rates can be achieved with acylated streptokinase than with high dose streptokinase but a similar systemic fibrinogenolytic response is observed. This is most likely due to deacylation of the substance and subsequent loss of fibrin selectivity in vivo.[42] Hence, in vivo, the thrombolytic profile of APSAC is almost indistinguishable from native streptokinase. Furthermore, APSAC has not demonstrated any convincing superiority over streptokinase in acute myocardial infarction and the additional drawbacks of streptokinase (antigenicity, hypotensive effects, and pyrogenicity) are maintained in the chemically modified substance.[31,43]

Thrombolytic Therapy in Humans – Review

The major indication for the use of thrombolytic agents in humans is myocardial infarction, with selective use in patients with pulmonary thromboembolism, peripheral arterial occlusion, deep vein thrombosis (DVT), and stroke.[27] Myocardial infarction, DVT and stroke are rarely reported in veterinary medicine and are not addressed in this review, but pulmonary thromboembolism and systemic arterial occlusion occur in both human and veterinary patients. Discussion of evidence supporting the use of thrombolytic agents in humans will, therefore, be limited to these conditions.

• Pulmonary Thromboembolism

In human medicine, thrombolytic agents have been shown to promote effective resolution of pulmonary arterial thrombi within a few hours, in comparison to a

more prolonged spontaneous resolution in untreated patients or patients treated with heparin alone.[44,45] Thrombolytic therapy is likely to be most beneficial to those patients with life-threatening PTE who are unlikely to survive without rapid reperfusion.

The majority of human deaths due to pulmonary embolism occur within a few hours of the onset of symptoms.[12,44,46] In order to decrease the mortality associated with these cases, rapid administration of appropriately directed therapy is necessary. Early hemodynamic benefits of chemical thrombolysis include reduction in elevated pulmonary arterial pressure, improved right ventricular function, and restored pulmonary perfusion.[44,45] A survival advantage has been documented in human patients with massive pulmonary thromboembolism associated with right ventricular dysfunction and hemodynamic instability when treated with heparin and streptokinase versus heparin alone.[47]

The benefit of thrombolytic therapy in hemodynamically stable patients with pulmonary thromboembolism has also been examined.[48-50] Sharma, et al evaluated 40 such patients with pulmonary thromboemboli treated with heparin alone, or in combination with either urokinase or streptokinase.[50] Normal pulmonary capillary blood volume was documented at both two weeks and one year after commencement of therapy in the group that received thrombolytic agents, in comparison to subnormal values in the heparin-treated group. The majority of subsequent studies comparing the effects of thrombolytic agents followed by heparin to heparin alone, however, have failed to support sustained benefits of thrombolytic therapy or significant differences in mortality rate.[45,49,51-54]

Konstantinides, et al reviewed the use of thrombolytic therapy in a subset of hemodynamically stable patients presenting with pulmonary thromboembolism and evidence of right ventricular dysfunction.[44] Mortality at 30 days was significantly lower in the 169 patients that underwent thrombolysis (4.7%), than in the 550 patients that received heparin alone (11.1%). In addition, recurrent PTE was less frequent in the group receiving thrombolytic therapy (7.7% versus 18.7%). Right ventricular dysfunction was found to occur in approximately 40% of hemodynamically stable human pulmonary thromboembolism patients and was associated with a doubling of the mortality rate at 14 days and a 1.5 fold higher mortality at three months. The study by Konstantinides, et al provides support for the use of thrombolytic therapy in this subset of patients but this recommendation is currently controversial in human medicine.[27]

In summary, human patients with pulmonary thromboembolism are categorized according to hemodynamic stability and presence of right ventricular dysfunction in order to facilitate decisions regarding the use of thrombolytic therapy. In patients with shock due to massive PTE, there is evidence that thrombolytic therapy reduces mortality, probably due to rapid restoration of pulmonary blood flow and improved right ventricular function.[47]

In patients who are hemodynamically stable, however, thrombolysis has not been found to significantly reduce the mortality or risk of recurrent PTE with the exception of the subset of patients with evidence of right ventricular dysfunction.

• Arterial Thromboembolism

The majority of human arterial thromboses are associated with atherosclerotic plaques.[55] Arterial thromboemboli unassociated with plaques most commonly arise in the left heart and are seen with atrial fibrillation, valvular heart disease or endocarditis, and in patients following artificial valve replacement or aortocoronary bypass surgery. With regard to the preferred sites of embolization, one study of humans with mitral valve disease reported that 75% of the emboli were cerebral and 25% were in the arteries of the limbs.

Most experience with arterial thrombolysis in human medicine has been gained using streptokinase. Clearance of the affected artery is obtained in approximately 67% of cases of recent occlusion (less than 72 hours) treated by intensive and prolonged thrombolysis (up to 72 hours).[56]

Thrombolytic agents are also thought to have therapeutic potential in improving the function in limbs with chronic arterial thromboses. Best results are achieved in patients with occlusive lesions of the large pelvic arteries and iliac arteries. The success rates of clearance of occlusions between six weeks and three months following the onset of clinical signs are approximately 30% in the femoral arteries and 40% in the iliac arteries.[57]

• Heparin

Heparin is not a thrombolytic agent, but because fibrinolytic agents do not prevent formation of a new thrombus, anticoagulant therapy with intravenous unfractionated heparin or subcutaneous low molecular weight heparin (LMWH) is generally recommended after fibrinolytic therapy in humans.[58] Heparin accelerates the anticoagulant activity of antithrombin III, which decreases the tendency towards thrombus formation. Heparin is infused simultaneously with t-PA in the treatment of MI in humans, but for all other indications is started following thrombolytic therapy when the activated partial thromboplastin time (aPTT) has returned to less than 2.5 times the control value. Heparin is then used to maintain an aPTT of 1.5-2.5 times baseline. After 48 hours, subcutaneous heparin administration or oral coumadin therapy is commenced and continued for as long as there is a predisposition to arterial or venous thrombosis.

Veterinary Experience with Thrombolytic Agents – Review

• Streptokinase

Streptokinase treatment in cats: Streptokinase has been used to treat cats with both experimental and natu-

rally-occurring aortic thrombosis.[59-61] Killingsworth, et al investigated streptokinase therapy in seven cats with experimentally created aortic thrombosis that were dosed with 90,000 U for the first 30 minutes, followed by 45,000 U/h until euthanasia at three hours.[59] This dose reliably produced systemic fibrinolysis that was defined as a statistically significant difference between treatment and control cats in prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen, and thrombin concentrations. Thrombolytic response was not similarly predictable, however, and apart from two streptokinase-treated cats in which thrombolysis occurred, treated cats could not be distinguished from control cats based on angiograms or pelvic limb thermal circulatory index (a measure of perfusion in the pelvic limbs). Both groups demonstrated minimal perfusion of the pelvic limbs with no improvement over the 180-minute treatment period. Side effects were limited to minimal bleeding in two cats. A suggested reason for failure of streptokinase in this model was the release of vasoactive substances such as thromboxane A2 and serotonin from activated platelets which may cause vasoconstriction, reducing collateral blood flow.[62]

Ramsey, et al reported similarly disappointing results with streptokinase treatment of eight cats with naturally-occurring distal aortic thromboembolism or left atrial thrombosis secondary to myocardial disease.[60] The cats received a loading dose of 90,000 U of streptokinase over 30 minutes, followed by a maintenance dosage of 45,000 U/hr for variable intervals. The patients were monitored closely for electrolyte changes associated with reperfusion. All of the cats died suddenly during maintenance streptokinase infusion. Three cats exhibited electrolyte changes (hyperkalemia, hypocalcemia), four cats showed acute respiratory distress, and two displayed neurologic signs. Necropsy was performed in five cats, and right ventricular myocardial infarction was identified as a possible cause of death in one cat with left atrial thrombosis. The cause of death in the other seven cats was not determined.

A recent retrospective study of streptokinase administration in 46 cats with arterial thromboembolism provided data on a larger group of cats than previously reported.[61] Significant heart disease was diagnosed in 45/46 cats, and 21/46 cats had congestive heart failure. Total streptokinase dose per cat ranged from 18,857 U/kg to 158,529 U/kg (median dose 47,345 U/kg), and duration of infusion ranged from 1-28 hours (median 4 hours). The majority of the cats (76% or 35/46) received 90,000 U, IV over 30 minutes followed by a maintenance dosage of 45,000 U/hr. Twenty-five (54%) of the cats had return of pulses within 22-24 hours of treatment, and 15 cats (33%) were ultimately discharged from the hospital. Eighteen cats died in the hospital and 13 were euthanatized due to poor response to treatment or complications. Eleven cats (24%) developed signs of clinical bleeding including hematuria, decreased PCV, rectal and oral mu-

cosal bleeding, and bleeding from a catheter site. Three of the cats required blood transfusion. Hyperkalemia was confirmed in 14 cases and suspected in 2 cases, and was associated with a longer duration of streptokinase infusion. There was no difference in survival based on total dose of streptokinase, streptokinase dosage on a U/kg basis, or duration of streptokinase infusion. Higher dosage levels of streptokinase on a U/kg basis were not associated with a greater likelihood of development of either hyperkalemia or bleeding tendency. Cats that received either a larger total dose of streptokinase, or a higher dose based on U/kg bodyweight, were more likely to gain arterial pulses than those treated with lower doses, but return of motor function was not similarly predictable.

Streptokinase in dogs: Ramsey, et al described the treatment of arterial thromboembolism in four dogs with streptokinase.[63] The range of duration of clinical signs associated with thrombosis was 6 to 120 days. Dog 1 had a right atrial thrombus secondary to cardiac disease and was treated with a 250,000 U (approximately 5000 U/kg) intravenous loading dose, a 100,000 U/hr maintenance dose, and heparin anticoagulant therapy. Dogs 2, 3 and 4 had thrombosis of the distal aorta and were treated with a loading dose of 90,000 U (15,000-18,000 U/kg), followed by a maintenance dose of 45,000 U/h for periods varying from 1-12 hours. Dogs 2, 3, and 4 received allopurinol to decrease reperfusion injury associated with thrombolysis. Complete thrombus resolution was evident in Dogs 1, 3 and 4 after the respective administration of 3 (Days 1, 2 and 3), 2 (Days 3 and 7) and 1 (Day 3) doses of streptokinase. Partial thrombus resolution occurred in Dog 2 after 3 doses of streptokinase (Days 1, 2 and 3). Partial or complete resolution of clinical signs associated with the thrombosis was seen in all dogs. Side effects consisted of minor hemorrhage requiring no treatment other than cessation of streptokinase infusion in Dogs 1, 2 and 4. No signs related to antigenicity or reperfusion were reported.

• *Tissue Plasminogen Activator*
Tissue plasminogen activator in cats: Tissue plasminogen activator has been used to treat cats with naturally-occurring aortic thromboembolism.[64] Administration of t-PA at a rate of 0.25 to 1 mg/kg/h for a total dose of 1 to 10 mg/kg was associated with resolution of the primary thrombus on angiography. Forty-three percent of cats survived therapy and were walking within 48 hours of presentation, but 50% of the cats died during therapy. Of the cats that died, 70% died as a result of reperfusion injury (hyperkalemia and metabolic acidosis), 15% of congestive heart failure, and 15% of arrhythmia attributed to embolization of left atrial thrombi to coronary arteries.

Tissue plasminogen activator in dogs: Clinical use of t-PA in a canine patient was reported by Clare et al.[65] The dog was treated for acute distal aortic thrombosis

with bolus injections of 1 mg/kg every 60 minutes for a total of 10 doses. Approximately three hours after the tenth dose, a pulse could be palpated in one leg and detected with a Doppler probe in the other leg. Six days after admission, no femoral pulses could be palpated and 2 doses of 1.1 mg/kg of t-PA were administered as boluses given 60 minutes apart. Immediately following the second dose, femoral pulses were palpable bilaterally. With another two 0.7 mg/kg boluses given the next day, there was continued improvement in pulse quality. Nine days after the last dose, femoral pulses were palpable, the dog's gait was clinically normal, and the distal aortic thrombus was no longer visible on ultrasound. More recently, treatment of a dog with aortic thromboembolism with 1 mg/kg of t-PA over 60 minutes in addition to heparinization failed to lead to significant improvement in hindlimb perfusion.[66]

Adverse Effects of Thrombolytic Therapy

The most predictable side effect associated with use of thrombolytic agents is hemorrhage. The likely mechanism is lysis of protective hemostatic plugs, although depletion of clotting factors and loss of vascular integrity probably plays a role.[1] In addition, platelet function may be impaired due to the need for fibrinogen as a cofactor for platelet aggregation, resulting in impaired adhesion and decrease in aggregation response.[19] A meta-analysis of three human studies with pulmonary thromboembolism gave similar rates of hemorrhage for the three major thrombolytic agents (8.8%, 10.2%, and 13.7% for t-PA, urokinase, and streptokinase, respectively).[67] Intracranial hemorrhage is a major concern in the use of thrombolytic drugs in humans, with patients treated for cerebral thrombosis representing a particular risk.[68]

Hypotension occurs in 10-15% of humans treated with streptokinase, and allergic reactions consisting of pruritis, rash, or fever in 5%.[30] The incidence of anaphylaxis is approximately 0.1%.[30] Anti-streptokinase antibodies develop in humans approximately five days after commencement of therapy and persist for at least 6-12 months.[37] It is recommended that streptokinase not be used within a 4-year interval due to concern about decreased efficacy and safety.[34] Streptokinase antibody activities have not been determined in dogs or cats.

Reperfusion of ischemic myocardium has been associated with ventricular arrhythmias in humans treated with thrombolytic agents.[69] Electrolyte and metabolic abnormalities secondary to reperfusion of large areas of muscle mass, uncommonly reported in humans, appear to contribute substantially to mortality in small animals treated with thrombolytic agents for arterial thromboemboli.[59,63] Life-threatening hyperkalemia and metabolic acidosis may result when potassium and metabolic waste products such as lactate, which have accumulated in the interstitial and vascular spaces distal to the thrombus, are released into the systemic circulation thrombolysis.[70] Moore, et al documented hyperkalemia in 14/46 cats with aortic thromboembolism within 2-15 hours of streptokinase administration, and found that these cats were less likely to survive than those that remained normokalemic.[61]

Absolute contraindications to thrombolytic therapy in human medicine include active internal bleeding, previous hemorrhagic stroke, recent stroke or cerebrovascular event (within 1 year), known intracranial neoplasm, or suspected aortic dissection. Major contraindications include severe uncontrolled hypertension, known bleeding diathesis, current warfarin therapy, recent trauma (2-4 weeks), recent major surgery (<3 weeks), recent internal bleeding (<3 weeks), active peptic ulcer disease, organ biopsy, non-compressible vascular punctures, and prior exposure (within 4 years) to streptokinase or known allergy to streptokinase.[34,71,72] Presence of a thrombus in the left atrium is also a contraindication for use of thrombolytic agents in humans as dissolution of the thrombus can lead to generation of many smaller thrombi and widespread thromboembolic disease.[73]

Potential Uses of Thrombolytic Agents in Veterinary Medicine

• Pulmonary Thromboembolism

The incidence of pulmonary thromboembolism in dogs and cats is unknown, however, it is probably not an uncommon event in critically ill patients.[7,8,74-77] Pulmonary thromboembolism comprised 0.9% of all postmortem diagnoses in dogs at Colorado State University between 1985 and 1995.[7] This study likely underestimates the incidence of pulmonary thromboembolism because not all patients who suffer this condition subsequently die. Pulmonary thromboembolism has been reported in dogs with cardiac disease, heartworm disease, pancreatitis, neoplasia, sepsis, hyperadrenocorticism, immune-mediated hemolytic anemia, diabetes mellitus, glomerulonephritis, and renal amyloidosis.[7,77-86]

Johnson, et al reported 29 dogs with necropsy-confirmed PTE.[7] Twenty-six dogs died during hospitalization; 11 died within 15 days of hospitalization (mean 6.1 +/- 4.9 days, median 4 days), and 15 were euthanatized within 17 days (mean 4.9 +/- 4.3 days, median 4 days). The remaining three dogs died within 34 days. In a study of 29 cases of necropsy-confirmed pulmonary thromboembolism in cats, associated conditions included cardiac disease (12), neoplasia (10), disseminated intravascular coagulation (5), protein-losing nephropathy (4), protein-losing enteropathy (4), immune-mediated hemolytic anemia (2), and sepsis (2).[8]

There are no published clinical studies reporting the thrombolytic treatment of pulmonary thromboembolism in dogs and cats. As is the case in humans, thrombolytic

therapy may be indicated in dogs and cats when pulmonary thromboembolism is accompanied by right ventricular dysfunction.

• *Systemic Thromboembolism*

Systemic arterial thromboembolism is seen most commonly as a complication of cardiomyopathy in cats. Laste and Harpster reviewed 100 cases of feline distal aortic thromboembolism in which 62 of 63 cats that underwent echocardiography had some form of cardiomyopathy.[87] Of the 100 cases, only 37% survived the initial thromboembolic event. Left atrial enlargement and stasis of blood in the left atrium appear to be important factors initiating thrombus formation in cats with predisposing cardiovascular disease.[64,87] The distal aorta is the most common site of emboli but brachial, mesenteric and renal arteries may be affected.

Aortic and iliac thromboembolism have also been reported in dogs in association with dilated cardiomyopathy, glomerulonephropathy, neoplasia, protein-losing enteropathy, endocardiosis, endocarditis, atherosclerosis, dirofilariasis, hyperadrenocorticism, pancreatitis, and hepatic disease.[66,79,81,83,85,88] In addition, thrombosis of the portal vein has been reported in dogs in association with pancreatic necrosis, peritonitis, distant neoplasia, or following therapy with glucocorticosteroids.[89] Cranial vena caval thrombosis was documented in one dog with concurrent aortic thromboembolism.[79] The majority of veterinary experience with thrombolytic agents to date has been with treatment of arterial thromboemboli and use of both streptokinase or t-PA in small numbers of dogs and cats.

• *Dosing of Thrombolytic Agents*

Experience with thrombolytic agents in dogs and cats is extremely limited and clinical data is only available for streptokinase and t-PA in the treatment of aortic thromboembolism and cardiac thrombosis. Major factors influencing choice of thrombolytic agents in human medicine include previous treatment with streptokinase or APSAC, duration of clinical signs, and cost of treatment. Tissue plasminogen activator has been shown to be more efficacious in the dissolution of aged thrombi but streptokinase is still used frequently in human hospitals due to cost effectiveness.[30] The current cost of streptokinase for treatment of a cat is approximately $160, in comparison to $800 for t-PA.[61]

The dose regimen which has been most frequently used for streptokinase administration in cats is 90,000 U IV over 30 minutes, followed by a maintenance dosage of 45,000 U/h IV for various intervals.[59-61] Early clinical studies by Ramsey, et al indicated that this dose was unsafe in cats.[63] However, in the recent study by Moore, et al, a similar regimen (used in 35/46 cats treated) was not associated with such devastating mortality.[61] The results of thrombolytic therapy should be compared with the prognosis in cats treated with supportive care alone.

It is reported that gradual return of motor function occurs over 4-6 weeks in 50% of cats treated with supportive care that survive the initial thromboembolic episode.[64,90] Further experience with streptokinase in cats is needed for estimation of a risk-to-benefit ratio for treatment of aortic thromboemboli. It is possible that, as with human PTE, classification of cats according to clinical parameters may allow identification of subgroups of cats more likely to benefit from therapy.

The successful use of streptokinase in four dogs by Ramsey, et al resulted in a recommended loading dose of 90,000 U (administered during a period of 20 to 30 minutes), followed by a maintenance rate of 45,000 U/h IV for 7-12 hours.[63] Three doses may be administered during a 72-hour period, but the efficacy and safety of the use of streptokinase for more than 72 hours are unknown.[63]

Currently, the small number of animals treated with varying protocols makes it impossible to provide safe and effective dose recommendations for t-PA. There is no dosage information available regarding the clinical use of urokinase, scu-PA and APSAC in small animals at this time.

Heparin is commonly administered to veterinary patients during the acute stages of systemic or pulmonary arterial thromboembolism. The goal of this therapy is to reduce the addition of new thrombus and shift toward a net thrombolytic state. Heparin therapy could be used in veterinary patients following the completion of thrombolytic treatment as discussed previously for human patients.

• *Monitoring Thrombolytic Therapy*

Clinical parameters that should be monitored during infusion of the thrombolytic agent include heart rate, respiratory rate, body temperature, central venous pressure, arterial blood pressure, packed cell volume (PCV) and total solids.[61,65] Serum electrolytes, arterial or venous blood gas analysis, and coagulation parameters including PT, aPTT, fibrinogen, and FDP concentrations should be performed both prior to and following infusion of the thrombolytic agent. Patients should also be observed closely for signs of hemorrhage such as hematuria, bleeding from catheter sites, and oral or rectal mucosal bleeding, as well as dyspnea, and changes in neurologic status.

The risk of hemorrhage associated with thrombolytic therapy can be minimized by avoiding phlebotomy, arterial puncture, or other invasive procedures. If bleeding occurs, management depends on the location, severity, and cause. Bleeding from vascular sites can usually be controlled with manual pressure.[67] Clinically significant hemorrhage requires discontinuation of treatment and administration of cryoprecipitate and/or fresh frozen plasma to reverse the associated coagulopathy.

Summary

Thrombolytic agents available in human medicine include streptokinase, urokinase, t-PA, scu-PA and APSAC, but clinical experience in small animals is limited to streptokinase and t-PA. The paucity of reports concerning veterinary patients may be attributed to difficulty in diagnosis of thromboembolic disease, lack of established protocols, limited reports of use in experimental and clinical settings, and cost associated with the drugs. Successful streptokinase use has been documented in a small number of canine patients with systemic thromboembolism.[63] Thrombolytic therapy is relatively efficacious in cats with aortic thromboemboli but is associated with a high mortality rate.[59,60,64] Future goals for thrombolytic therapy in veterinary medicine include determination of more specific clinical indications, as well as design of effective protocols that minimize mortality and morbidity.

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