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Primary hemostasis

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Abstract

Objective: To review the current understanding of the mechanisms responsible for primary hemostasis and to give an overview of primary hemostatic syndromes in small animal patients. Current and future therapeutic options for dysfunction of primary hemostasis are discussed.
Data sources: A thorough search of the human and veterinary literature using the keywords platelets, primary hemostasis, von Willebrand factor (vWF), von Willebrand disease, aspirin, thromboxane, and aggregation, were performed. Databases searched included OVID Medline, Pubmed, and CAB abstracts.
Conclusions: Primary hemostasis occurs when platelets adhere to an injured or disrupted endothelial surface. Adherence is followed by activation, or the release of platelet granule contents. The agonists released from platelet granules recruit additional platelets and induce their activation and aggregation. Adhesion, activation, and aggregation are mediated by different receptors and ligands depending on the local blood flow conditions. vWF and adenosine diphosphate are the primary mediators of adhesion, activation, and aggregation under high shear conditions. During low shear conditions collagen, fibronectin, and laminin mediate adhesion, thromboxane A_2 promotes activation, while aggregation is mediated by glycoprotein Ib-IX-V (GP Ib–IX–V) and fibrinogen. Knowledge of the receptor interactions during different blood flow conditions is crucial to the understanding of the various inhibitors of primary hemostasis available to clinicians.

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Introduction

Normal hemostasis occurs in 3 steps. Primary hemostasis occurs when platelets adhere to a damaged or disrupted endothelium. This occurs frequently throughout life, not only with injury to blood vessels (venipuncture) but also during normal endothelial cell turnover (endothelial cell death). In addition, infectious agents, acidosis, hypoxia, inflammation, and hypotension all have the ability to cause damage to the endothelium.[1] During adhesion to the damaged endothelium, platelets bind and undergo changes that allow platelets to adhere to each other, forming a temporary platelet plug. The platelet plug is only stable for a few hours if the secondary hemostatic forces do not solidify and reinforce the plug with a crosslinked fibrin meshwork. The last stage in coagulation occurs when plasminogen is activated to plasmin, which breaks down the fibrin and removes the clot in a process called fibrinolysis.

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The various mediators and ligands responsible for primary hemostasis are activated under either high shear, low shear, or all shear conditions. An understanding of the process of activation during different types of shear stress is crucial to understanding the efficacy of the various inhibitors of primary hemostasis.

Disorders of hemostasis are common in veterinary medicine and many diseases are now being shown to predispose animals to a hypercoagulable state. Cardiac disease, renal disease, neoplasia, severe necrotizing pancreatitis, immune-mediated hemolytic anemia, hypercortisolism, atherosclerosis, diabetes mellitus, and sepsis have all been implicated to increase thrombotic risk in companion animals.[2] Inhibition of primary hemostasis, either intentional (aspirin) or as a side effect of commonly used medications (non-steroidal anti-inflammatory drugs; NSAIDs), is a growing concern in veterinary medicine and knowledge of the pathways responsible for this inhibition are crucial to the understanding and treatment of these diseases.

Primary Hemostasis

Human platelets have a 5–7 day lifespan and are approximately 2–5 μm in diameter,[3] while canine platelets

have an average lifespan of approximately 6 days.[4] Platelet synthesis occurs predominantly in response to thrombopoietin, which is synthesized in bone marrow and smooth muscle cells.[5] Elimination of thrombopoietin from the circulation occurs via adsorption onto platelets, providing a negative feedback mechanism.[5] The ability of the platelet to respond to such a wide variety of stimuli, despite its lack of a nucleus, is due, in part, to the abundance of substances contained in the platelet. Preformed substances exist in platelets within alpha and delta (dense) granules. Alpha granules contain platelet derived growth factor, fibronectin, transforming growth factor β, β-thromboglobulin, platelet factor 4, fibrinogen, factors V and VIII, and adhesive proteins such as von Willebrand factor (vWF).[6] Dense granules contain adenosine diphosphate (ADP), adenosine triphosphate (ATP), histamine, epinephrine, serotonin, and calcium ions.[7] Platelets also contain actin, myosin, thrombosthenin (contractile protein), mitochondria, enzyme systems (that form ADP, ATP, and prostaglandins), fibrin stabilizing factor (factor XIII), growth factors (which facilitate the growth of vascular endothelial cells, vascular smooth muscle cells and fibroblasts), endoplasmic reticulum, and golgi.[5]

Prevention of adherence to normal endothelial cells is facilitated by a combination of physical factors and biochemical factors. Physical factors include repulsive forces from electronegative charges on platelets and endothelial cells. Biochemical factors include synthesis of inhibitors of platelet activation such as nitric oxide (NO) and prostacyclin.[8] Nitric oxide and prostacyclin are released constitutively from the endothelium and act locally to prevent platelet adhesion to normal endothelium. There are also substances expressed on the endothelial cell surface that degrade or inhibit platelet agonists. These include ADPases, heparan sulfate, and thrombomodulin.[8]

Platelet Adhesion, Activation, and Aggregation

Platelet adhesion to exposed subendothelium is a complex process that involves multiple adhesive ligands and receptors.[9] Most of the research investigating platelet adhesive properties has been done *ex vivo*. This is a crucial point since these adhesive properties have been shown to be dependent on the local blood flow conditions in the body.[9] For instance, the interaction of vWF and platelets occurs only under high shear conditions.[9] In general, conditions of high shear are thought to be present in small- and medium-sized arteries and low shear conditions are present in large arteries and all veins. Data from studies conducted during specific shear conditions cannot necessarily be applied to conditions of different shear stress.

Platelet activation is the process where platelets change shape, release the contents of alpha and dense granules, and express receptors on their surface to facilitate platelet aggregation.[3] Platelet activation can occur secondary to adhesion or can occur independent of adhesion as when thrombin is generated via inflammation. Thrombin then induces platelet activation before adhesion has occurred. Platelet aggregation occurs when platelets interact with one another to provide the catalytic surface necessary for thrombin generation and subsequently fibrin formation, which stabilizes the hemostatic plug[8] (Figure 1).

During high shear conditions, initial platelet adhesion to exposed subendothelial connective tissue is primarily mediated by collagen and vWF. vWF contributes to thrombus formation in 2 ways: by mediation of adhesion of platelets to the extracellular matrix and each other, and by protecting factor VIII from rapid clearance from plasma.[8] vWF is an adhesive protein synthesized by megakaryocytes and endothelial cells.[10] It is stored in secretory vesicles called Weibel–Palade bodies in endothelial cells and in alpha granules in megakaryocytes and platelets.[8] Release of vWF can be stimulated by several substances including thrombin, fibrin, vasopressin, collagen, platelet-activating factor (PAF), epinephrine, and histamine.[10] After release from Weibel–Palade bodies, vWF may enter the bloodstream or become bound to collagen in the subendothelium. Larger multimers of vWF appear to be more hemostatically active than smaller ones.[8] There are 2 distinct receptors for vWF on platelets, the Integrin $\alpha_{IIb}\beta_3$ receptor (formerly called the GP IIb–IIIa complex) and the GP Ibα in the GP Ib–IX–V complex.[8] The latter is a surface integrin receptor located along the cell surface that, upon activation, undergoes a shape change to express a binding site for fibrinogen.[11] After endothelial damage, exposure of subendothelial collagen occurs and vWF attaches to the exposed collagen, releasing factor VIII.[3] Platelets then appear to roll along the endothelium similar to leukocyte rolling.[12–14] This rolling is initiated by the platelet GP Ibα receptor attaching in a very loose way to vWF on the subendothelium and mediated by the expression of P-selectin on activated endothelial cells.[15] These attachments are very brief and frequent, presumably due to a fast dissociation rate and a short half-life of the bond between GP Ibα and vWF.[8]

Once platelets attach to the endothelium via vWF and collagen they undergo a conformational change with exposure of the Integrin $\alpha_{IIb}\beta_3$ receptor.[14] Stimulation by subendothelial collagen causes platelets to expose and assemble membrane glycoproteins, which can then bind fibrinogen and vWF, cofactors for platelet recruitment and aggregation.[3]

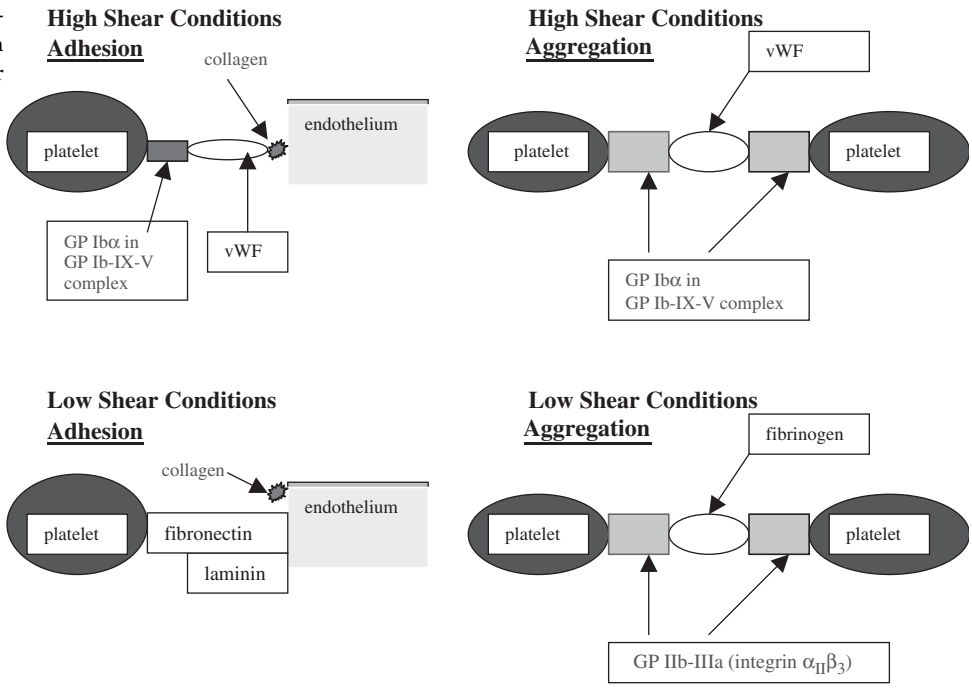

Figure 1: An overview of platelet adhesion and aggregation under high shear and low shear conditions.

Under low shear conditions, platelet adhesion to subendothelium occurs via collagen, fibronectin, and laminin.[16–21] After adherence, under all shear conditions, platelets then undergo a shape change and form intraplatelet bridges. This leads to activation, the process whereby degranulation of platelet contents occurs to release agonists. Platelet activation by thrombin, collagen, ADP, and thromboxane A_2 (TXA_2) is induced by initiation of a pathway that elevates the cytosolic-free calcium concentration in the platelet.[22–25] In response to elevated calcium, platelets release agonists from alpha granules and dense bodies (ADP, serotonin, epinephrine). They also synthesize PAF and TXA_2. These agonists recruit additional platelets and induce their activation and adhesion to the platelet plug.

Platelets are capable of eicosanoid synthesis. The major eicosanoids from human platelets, TXA_2 and 12-HETE,[26] are not stored, but synthesized *de novo* from arachidonic acid (AA). The biology of 12-HETE is poorly understood.[26] TXA_2 is a major platelet aggregator and vasoconstrictor, and is formed when AA is released from membrane lipids on the platelet by the actions of phospholipase A_2, prostaglandin H synthase, and thromboxane synthase.[26] Once formed, TXA_2 diffuses across cell membranes to induce platelet aggregation. Due to its short half-life (30 seconds), the potent effects of TXA_2 are short lived and remain local.[22]

Under high shear conditions, ADP promotes platelet activation, while under low shear conditions, it is TXA_2 that causes activation.[27–29] Thrombin promotes platelet activation under all shear conditions via activation of the GP Ib–IX–V complex and the protease-activated receptors (PARs).[9] Thrombin is the most potent physiological activator of platelets known.[3] While the secretory response of platelets to collagen, ADP or epinephrine can be inhibited by inhibitors of cyclooxygenase (i.e. aspirin), the response to thrombin is largely independent of cyclooxygenase inhibition. Therefore, thrombin is classified as a *strong* platelet agonist, while ADP and epinephrine are *weak* agonists.[30]

Platelet aggregation can be stimulated by thrombin, ADP and by secondary feedback via TXA_2 from platelets.[30] Platelet aggregation is mediated by Integrin $\alpha_{IIb}\beta_3$ and GP Ib–IX–V receptors, with the latter playing a more important role as blood flow increases.[31] At high shear flow rates, vWF mediates platelet aggregation, while at low shear flow, fibrinogen is the primary ligand of thrombus growth.[31]

Activated platelets provide a template via the Integrin $\alpha_{IIb}\beta_3$ receptor for the assembly of coagulation factors for the formation of crosslinked fibrin meshwork (secondary hemostasis).[3] After the platelet plug has bridged the gap between endothelial cells, adjacent endothelial cells release prostacyclin causing vasodilation and decreased platelet aggregation. This release of prostacyclin stops the platelet plug from growing out of control. How the endothelium is repaired beneath the platelet plug is still somewhat of a mystery. It has recently been suggested that endothelial progenitor cells that are mobilized from the bone marrow and travel to sites of vascular injury may be responsible for the maintenance and repair of endothelial function in blood vessels.[32]

Many of the substances released from platelets are capable of inducing and propagating an inflammatory state and it is now apparent that platelets play a crucial role in inflammation via the production of cytokines (interleukin-1), release of PAF and serotonin, and via their interaction with neutrophils.[7] In addition, circulating platelets can be directly activated by certain bacteria or other infectious organisms including immune complexes.[7] Several experimental studies have demonstrated 2 different techniques that platelets use to engulf bacteria.[7] Platelet aggregates are formed upon contact with bacteria and appear to encircle the bacteria and release their contents into the center of the formed aggregate onto the trapped bacteria. Additionally, phagocytosis appears to occur when platelet numbers are too low to allow aggregation. Bacteria are phagocytized by platelets and the platelet cytoplasmic granules release their products to the bacteria.[7] There are numerous ways that inflammatory cells attract platelets. Cathepsin G, released by neutrophils, is a strong platelet agonist.[33] Platelet activation appears to be an early event in inflammation and much ongoing research is focused on the area of 'crosstalk' between coagulation and inflammation.[6]

Two endogenous substances that play a critical role in maintaining an 'anti-coagulant state' by decreasing platelet reactivity are NO and prostacyclin. Prostacyclin and NO, which are released from endothelial cells, are potent platelet inhibitors that appear to act synergistically to inhibit platelet aggregation.[34] Nitric oxide inhibits platelet activation, adhesion, and aggregation and is, itself, inhibited by reactive oxygen species. Increasing available NO is the main mechanism whereby anti-oxidants decrease platelet activity.[31]

Syndromes Affecting Primary Hemostasis

Primary hemostatic defects can be separated into 3 categories: thrombocytopenia, thrombocytopathia, and vasculitis or endothelial disruption. Thrombocytopenia can result from decreased platelet production, increased destruction, or sequestration. Decreased production can be caused by drugs (e.g. Trimethoprim sulfa), infections, myelodysplasia or it may be idiopathic.[35] Destruction of platelets occurs most commonly by immune-mediated diseases, but can also be caused by bacterial or viral infections, or neoplasia. Sequestration of platelets occurs with splenic diseases or splenomegaly and can also occur during endotoxemia.[35]

Thrombocytopathia, a functional platelet defect, can be either an acquired or inherited condition. Acquired thrombocytopathia occurs with Ehrlichiosis, feline leukemia virus infection, envenomation, liver disease, neoplasia, uremia, or from drugs such as aspirin.[35] von Willebrand's disease (vWD) is thought to be the most common inherited primary hemostatic defect in dogs.[36] vWF performs 2 major hemostatic roles; it is a carrier protein for factor VIII, protecting it from proteolysis by protein C and it mediates adhesion of platelets to damaged endothelium.[37]

There are 3 forms of vWD recognized in dogs. Dogs with Type 1 vWD have all multimers present but at decreased numbers. In Type 2, the large multimers are absent and in Type 3, all multimers are absent. Plasma vWF is an acute phase reactant and is increased during times of stress.[38–41] vWF is found in 3 areas: the subendothelial matrix; circulating in plasma; and in the alpha granules of platelets and megakaryocytes. Large multimers of vWF are secreted by endothelial cells into plasma where they are processed into smaller multimers that do not interact with platelets.[42] The large multimers aggregate platelets to a much greater degree than the smaller ones. The largest multimers are found only transiently in the circulation due to rapid cleavage into smaller multimers and efficient elimination processes.[42] Regulation of multimer size is crucial to appropriate hemostasis and a defect in cleavage of large multimers is responsible for the escalating thrombosis seen in the hemolytic-uremic syndrome.[43] The syndrome is characterized by hemolytic anemia, thrombocytopenia, azotemia, neurologic changes, and fever.[44] In humans, the most common cause is ingestion of a shiga toxin producing strain of bacteria, usually *E. Coli* 0157:H7.[45] This syndrome has been reported in a dog.[46] The deficiency of vWF cleaving protease causes accumulation of large multimers in circulation and subsequent platelet aggregation.[47,48] A deficiency of vWF cleaving protease along with accumulation of large multimers of vWF has also been found in patients with disseminated carcinoma and melanoma.[49] Several agents can stimulate the release of vWF from Weibel–Palade bodies including desmopressin acetate (DDAVP), epinephrine, thrombin, and histamine.[37] Desmopressin acetate, a synthetic analog of vasopressin with minimal vasopressor activity, causes release of vWF from endothelial cells and release of factor VIII from storage sites.[50,51] The increase in vWF and factor VIII decreases over a 24-hour time period with subsequent doses of DDAVP. There is approximately a 30% decrease seen with the second injection reported in humans.[52] Repeated doses are more likely to cause tachyphylaxis. In veterinary medicine, the intranasal preparation can be given subcutaneously at 1 U/kg. The peak onset of vWF release is expected to be within 10 minutes of intravenous injection and is reported to last approximately 2 hours.[53]

Cryoprecipitate is a form of fresh frozen plasma (FFP) that concentrates fibrinogen, factor VIII, and vWF

into a smaller volume. Both fresh whole blood and FFP contain fibrinogen, factor VIII and vWF, and can be used to treat a bleeding vWD patient. The benefit of cryoprecipitate is that it is concentrated and can, therefore, be delivered in a smaller volume, avoiding volume overload. The dose is 1 U/10 kg for cryoprecipitate and 10 mL/kg for FFP. Frozen or stored plasma (plasma that has not been frozen within 6 hours of collection or has been thawed and refrozen) is not appropriate for the treatment of vWD-induced bleeding since it loses the 'labile' clotting factors, V and VIII.[53]

Heparin-induced thrombocytopenia (HIT) is a syndrome seen frequently in human patients. There are 2 forms of HIT seen in humans. Type I HIT is a non-immunologic process where heparin binds directly to the platelet surface. There is a mild decrease in the platelet count due to increased clearance of platelets.[54] The effect on platelet number is dependent on the size and charge of the heparin molecules, which is why this type of HIT is generally not seen with the low molecular weight heparins (LMWH). There is usually a spontaneous rebound of the platelet count with type I HIT upon discontinuation of heparin.

Type II heparin-induced thrombocytopenia and thrombosis (HITT) is an immunologically mediated process, which appears to be due to antibodies to heparin that then complex to platelets. Platelet aggregates are formed but the degree of aggregation varies widely among humans.[54] Thrombosis, which is the most devastating consequence of Type II HITT, can occur due to these aggregates. It is the thrombotic risk that differentiates HITT from other drug-induced thrombocytopenias.[54] HIT syndromes have not been reported in veterinary patients.

Vasculitis or damage to endothelial cells can be the result of infection (i.e. endotoxin, *Rickettsia rickettii*, *Leishmania*, feline infectious peritonitis), heartworm disease, heatstroke, drug toxicity, immune-mediated disease or neoplasia.[55] Endothelial cell damage can lead to dysfunction or inadequate numbers of endothelial adhesion receptors, affecting platelet function.

Inhibitors of Primary Hemostasis

With advancing knowledge of platelet function, pharmacologic manipulation of platelet function has also advanced and several novel platelet inhibitors are either in clinical trials or are in development. As mentioned previously, low and high shear states play an important role in platelet function and, therefore, the class of platelet inhibitor appropriate for the clinical situation will vary. Combination therapy utilizing more than one drug class is becoming more popular and appears to be the most efficacious in a broad range of clinical settings where shear stress varies among patients. A brief review of the current classes of platelet inhibiting drugs is presented below.

Thromboxane Inhibitors

Aspirin is the prototypical thromboxane inhibitor and so far it has not been possible to improve upon aspirin's TXA_2 inhibitory effects.[56] Platelets' lack of a nucleus becomes important with drugs such as aspirin that inhibit the cyclooxygenase enzyme for the life of the platelet because new proteins cannot be re-synthesized.[57] In platelets, aspirin irreversibly inhibits cyclooxygenase through acetylation of a serine residue of key importance for the function of the cyclooxygenase system. This acetylation causes inhibition of TXA_2 and serotonin.[57] Normal function is restored 5–10 days after a single dose of aspirin (platelet lifespan approximately 7–10 days). Since new platelets are produced daily there is a gradual increase in function over this time period.[57]

In endothelial cells, aspirin also inhibits cyclooxygenase. These cells, however, tend to favor prostacyclin production. Prostacyclin is the most potent endogenous platelet inhibitor and inhibits aggregation in response to all known agonists, including the most potent agonist, thrombin.[26] When aspirin inhibits both platelet thromboxane and endothelial prostacyclin, there is no reduction in platelet aggregation. Some suggest that there may actually be a tendency toward platelet aggregation since the most potent platelet agonist, thrombin, is not inhibited by aspirin.[26,57] Since platelets have no nucleus and endothelial cells do, endothelial cells can produce more cyclooxygenase. After exposure to aspirin the endothelial cell cyclooxygenase enzyme recovers activity within hours.[57] Giving low dose aspirin is thought to inhibit platelets but allow endothelial cells to continue to release prostacyclin due to their ability to create more cyclooxygenase.

When aspirin is administered orally, platelets in the portal circulation become exposed to relatively high concentrations. However, the aspirin is rapidly deacylated to salicylic acid in the liver and plasma by nonspecific esterases.[57] The systemic endothelium does not get exposed to the same 'high' dose as do the platelets in the portal circulation. This oral effect of aspirin allows low dose aspirin to act as a selective TXA_2 inhibitor without suppressing systemic prostacyclin synthesis.[57]

High dose aspirin (21 mg/kg orally every third day) decreased platelet aggregation in response to AA in cats in one study,[58] and decreased platelet aggregation in response to collagen in another study.[59] Median survival of cats with an episode of arterial thromboembolism treated with aspirin was higher (117 days) when compared with historical data on cats treated with warfarin (51 days), and there were more complications

in the cats treated with warfarin.[60] The authors concluded that low dose aspirin is a safe option for thromboprophylaxis in cats.

Ridogrel and terbogrel, both experimental drugs, are combined TXA_2 synthase inhibitors and TXA_2/prostaglandin endoperoxide receptor antagonists.[56] Although ridogrel appeared promising in preclinical trials, it did not show a significant benefit in a clinical trial in which the endpoint was improvement of angiographic patency.[61] Terbogrel is an orally administered drug, which was associated with severe leg pain in a large number of patients in clinical trials and was, therefore, not well tolerated.[62]

Therefore to date, the only readily available and proven thromboxane inhibitor is aspirin. This drug has been shown to be safe and effective at low doses (1 mg/kg orally q 24 h) in humans and cats.

Nitric Oxide – Non-steroidal Anti-Inflammatory Drugs

Although NO is a potent platelet inhibitor, NO donors, such as nitroprusside, have not been used specifically for platelet inhibition due to significant side effects (i.e. severe hypotension) Nitric oxide is crucial to gastrointestinal mucosal defense and appears to work in a similar fashion to prostaglandins.[63] A novel group of compounds, which link the NO-releasing moiety to a NSAID, are currently in human clinical trials.[63] NSAIDs interfere with the anti-coagulant effects of low dose aspirin. The NO–NSAIDs may prevent loss of this anticoagulant effect when the patient is concurrently taking NSAIDs. The theory behind these derivatives is that the NO is released locally in the stomach and provides local gastric protection. Systemic effects of NO (hypotension) have not been reported in healthy animals or healthy human volunteers.[64,65] The NSAID is absorbed systemically to provide the benefits of an NSAID without the undesirable gastrointestinal side effects of the NSAID alone. The data from 2 recent human clinical trials are consistent with experimental studies showing that NO–NSAIDs are devoid of the gastric toxicity seen with NSAIDs alone.[66,67]

Glycoprotein IIb–IIIa Inhibitors

The GP IIb–IIIa receptor appears to be the final common pathway to platelet aggregation and is, therefore, a prime target for inhibition.[56] Human clinical trials of several of the injectible forms (e.g. Eptifibatide,[a] Abciximab,[b] and Tirofiban[c]) appear promising.[68–71] There were disappointing results in trials with oral GP IIb–IIIa receptor inhibitors that showed an increase in major bleeding and no decrease in thrombosis.[72,73] It appears that these oral agents might promote thrombosis when present at trough levels and might promote hemorrhage when present at peak levels in the same patient, potentially devastating complications.[56]

Promising *in vitro* results were reported with eptifibatide on feline platelets.[d] Unfortunately, in a study on healthy research cats, the drug caused unpredictable circulatory failure and sudden death in some of the cats and the authors suggest that this is not an appropriate agent for cats.[e]

ADP Receptor Antagonists

The thienopyridines, clopidogrel[f] and ticlopidine[g], act via ADP receptor antagonism. Ticlopidine has been shown to cause neutropenia and thrombotic thrombocytopenic purpura.[56,74] Clopidogrel showed an 8.7% relative risk reduction in a human clinical trial when compared with aspirin.[75] Ticlopidine administered at a dose of 100 mg orally once per day was not effective in decreasing platelet aggregation in 8 healthy cats.[h]

Future Therapies

Combination therapy appears to be the most promising aspect of the future therapies due to the different blood flow conditions that control the activity of different receptors and ligands. The combination of the ADP receptor antagonist, clopidogrel, and the thromboxane inhibitor, aspirin, appears to be synergistic and has been shown to be superior to either of the 2 drugs alone in humans.[76,77] Other therapies that appear promising, and which will most likely be included in a combination approach, include anti-oxidants, platelet adhesion receptor inhibitors, and gene therapy.[56] All of these new therapies, individually and in combination, will have to be tested in small animals for safety and efficacy.

Conclusion

Clot formation begins with primary hemostasis, resulting in the formation of the temporary platelet plug. Primary hemostasis consists of platelet adhesion, activation, and aggregation and involves multiple receptors and ligands. Shear stress appears to play a major role in primary hemostasis with different receptors acting under low shear and high shear conditions. Inhibitors of platelet aggregation are classed according to their mechanisms of action. Newer therapeutics that combine several drugs targeting multiple pathways appear very promising for thromboprophylaxis in humans.

Footnotes

[a] Eptifibatide, Integrilin, COR Therapeutics, South San Francisco, CA.
[b] Abciximab, ReoPro, Eli Lilly & Co., Indianapolis, IN.
[c] Tirofiban, Aggrasat, Merck & Co., Inc., West Point, PA.

[d] Dowers K. Anti-aggregatory effects of a GPIIB/IIIA antagonist on feline platelet function. In: Proceedings of the 18th Symposium of the American College of Veterinary Internal Medicine. Seattle, 4–5 June 2000; p. 712.
[e] Bright JM, Dowers K, Hellyer P. Correspondence letter. J Vet Intern Med 2002; 16:fmv.
[f] Clopidogrel, Plavix, Bristol-Meyers Squibb, Princeton, NJ.
[g] Ticlopidine, Ticlid Tablets, Roche Laboratories, Inc., Nutley, NJ.
[h] Hogan DF, Andrews DA, Talbott K, et al. The pharmacodynamics and platelet responses to ticlopidine in the cat, In: Davenport DJ, Lester GD. eds. Proceedings of the 20th Symposium of the American College of Veterinary Internal Medicine, Dallas, 29 May–1 June 2002. 2002; p. 777.

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