Anticoagulation in Intermittent Hemodialysis: Pathways, Protocols, and Pitfalls

Sheri Ross, DVM, PhD

KEYWORDS

• Anticoagulation • Hemodialysis • Coagulation

The safety and efficiency of intermittent hemodialysis have improved dramatically over the past several decades. Despite this advancement, prevention of thrombosis in the extracorporeal blood circuit remains a significant challenge in many cases. During intermittent hemodialysis, the patient's blood is exposed to many substances, including the dialysis catheter, blood tubing, chambers and headers, and the large surface area of the dialyzer membrane. These surfaces exhibit variable degrees of thrombogenicity.[1] In order to deliver a safe and effective dialysis treatment, an appropriate level of anticoagulation must be achieved to prevent thrombosis of the extracorporeal circuit without causing excessive bleeding in the patient.

COAGULATION

Since the 1960s, the understanding of homeostasis has been based on the coagulation cascade model.[2] In this model, clotting mechanism is divided into 2 pathways. In each pathway, the clotting factors are proenzymes that can be converted to active enzymes. Coagulation may be initiated via an intrinsic pathway, so named because all the components are present within the blood, or an extrinsic pathway, in which tissue factor (TF), a subendothelial cell membrane protein, is required in addition to the circulating components. The initiation of either pathway results in activation of factor X and the eventual generation of a fibrin clot through a common pathway.[3]

The most recent model of coagulation is known as the cell-based model of coagulation. In this model, coagulation involves 3 phases: initiation, amplification, and propagation. A recent review of this subject has been provided elsewhere.[4] This model is

The author has nothing to disclose.
Departments of Nephrology, Urology, Hemodialysis, University of California Veterinary Medical Center – San Diego, 10435 Sorrento Valley Road, Suite 101, San Diego, CA 92121, USA
E-mail address: sro@ucdavis.edu

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a result of the discovery that exposure of blood to cells that express TF on their surface is both necessary and sufficient to initiate blood coagulation in vivo.[5] In the cell-based model, coagulation requires a cell, or cellular debris expressing TF and platelets. TF is not present on the surface of vascular endothelium but is present within the membranes of cells surrounding the vasculature, where it is exposed to blood only by disruption of the endothelium or activation of the endothelial cells or monocytes. Cellular microparticles (MPs) are membrane fragments derived from many different cell types during various states including remodeling, activation, and apoptosis.[6] These MPs have been shown to express TF, which may contribute significantly to thrombosis.[7] MP levels are already increased in patients with renal disease, but an even more dramatic increase occurs in patients undergoing hemodialysis; this further increase is primarily caused by platelet-derived MPs. Possible explanations for the increase in MP levels include complement activation within the dialyzer, shear effect of cells during transit through the catheter and extracorporeal circuit, and to a lesser extent, the presence of endotoxins in the dialysate.[8]

EFFECTS OF UREMIA ON COAGULATION

Although dialysis requires anticoagulation to prevent clotting in the extracorporeal circuit, it is important to recognize that many uremic patients have a bleeding diathesis. The pathogenesis of uremic bleeding is multifactorial and includes defects in all stages of platelet hemostasis, including adhesion, secretion, and aggregation. The platelet count is usually within the normal range or just slightly low in uremic patients (**Box 1**).[9,10] Although levels of von Willebrand factor (vWf) are usually normal or slightly elevated in patients with kidney disease, a functional defect in the interaction of vWf with glycoprotein IIb/IIIa complex in uremic patients inhibits platelet–vessel wall interactions, contributing to bleeding.[11] When compared with healthy controls, uremic patients also produce excessive prostacyclin and nitric oxide, and these elevated levels contribute to the bleeding diathesis.[12] Prostacyclin is a potent inhibitor of platelet aggregation and the most important modulator of the production of platelet cyclic AMP.[13] Nitric oxide is a potent modulator of vascular tone that limits platelet adhesion to the endothelium and platelet-platelet interaction by increasing the formation of cellular cyclic GMP.[14] In addition to uremia-associated bleeding diathesis, patients with uremia may also have comorbid conditions and/or receive medications that affect hemostasis and are therefore predisposed to bleeding complications.

COAGULATION AND EXTRACORPOREAL CIRCUITS

Both the TF and contact activation pathways may trigger clotting in the extracorporeal circuit. Turbulence and shear stress can cause platelet activation via the contact pathway and can ultimately lead to release of TF, or TF may be triggered directly through the TF pathway.[15] When the blood flow is slow, platelets can bind to fibrinogen adherent to the extracorporeal circuit thus precipitating clotting. During hemodialysis, platelets and leukocytes may aggregate on the dialyzer membrane. Once they adhere to the artificial surface, both cell types become activated and may express TF on their surface. The composition of the dialyzer membrane seems to influence the extent of adherence and activation.[16]

Within the extracorporeal circuit, not only the dialyzer membrane but also the dialysis catheter, blood lines, dialyzer headers, and arterial and venous pressure chambers contribute to the risk of thrombogenesis. The arterial and venous pressure chambers are particularly thrombogenic because of the blood-air interface and the potential for stagnation of blood flow. The likelihood of circuit clotting also increases

Box 1
Some factors affecting hemostasis in uremic patients

Platelet-related factors

Defective activation of glycoprotein IIb-IIIa receptors

Abnormal intracellular calcium mobilization

Reduced intracellular ADP and serotonin levels

Decrease in dense granule content

Vessel wall–related factors

Abnormal platelet adhesion

Decreased von Willebrand factor activity

Enhanced nitric oxide and prostacyclin production

Blood-related factors

Anemia

Erythropoietin deficiency

Altered blood rheology

Other factors

Drugs: β-lactam antibiotics, nonsteroidal antiinflammatory drugs, antiplatelet agents, anticoagulants

Comorbid conditions: gastrointestinal ulceration

Invasive procedures: surgery, biopsy, feeding tube, intravenous catheter placement

Uremic toxins

with hemoconcentration caused by dehydration, excessive ultrafiltration, or the administration of packed red blood cells (**Box 2**).[15]

PARAMETERS FOR ASSESSING CLOTTING IN THE EXTRACORPOREAL CIRCUIT

Careful monitoring of the extracorporeal circuit during dialysis may provide many indicators of potential clotting problems (**Box 3**). The simplest method of evaluation is visual inspection (**Fig. 1**). Very dark blood within the circuit, streaks within the dialyzer, or the presence of fibrin on the walls of the arterial or venous chambers may indicate clotting and should be further evaluated by flushing the circuit with saline while temporarily occluding the arterial blood line. Flushing the circuit allows not only for a better assessment of the degree of clotting in the dialyzer and chambers but also the inspection of the arterial header. After every treatment, the patient's dialyzer should be closely inspected and the degree of fiber clotting recorded. This information may be used to adjust the anticoagulation regime for subsequent treatments. The degree of dialyzer clotting for 2356 individual dialysis treatments at 3 veterinary dialysis centers (University of California Davis College of Veterinary Medicine, University of California Veterinary Medical Center – San Diego, and Animal Medical Center) is presented in **Fig. 2**.

The extracorporeal circuit pressures, typically measured in the arterial and venous pressure chambers, may also indicate clotting problems. An increase in the postpump arterial pressure combined with a decrease in the venous pressure indicates the

Box 2
Technical or mechanical factors that may contribute to clotting in the extracorporeal circuit

Blood-related factors

Low blood flow rates

Inadequate blood flow due to catheter positioning or access recirculation

Frequent interruption of blood flow due to machine alarm conditions

High ultrafiltration rate

High hematocrit

Intradialytic transfusion of blood products

Circuit-related factors

Retained air in dialyzer or lines due to inadequate priming

Inadequate priming of heparin infusion line

Biocompatibility of dialyzer membrane

Anticoagulation-related factors

Inadequate loading dose of heparin

Insufficient time lapse after loading the dose for systemic anticoagulation

Inadequate dose/setting of the heparin constant rate infusion pump

Delayed starting of heparin pump/failure to release line clamp

Early termination of heparin constant rate infusion

presence of clotting in the arterial chamber or the dialyzer. An increase in the venous pressure could indicate clotting in the venous return line or a problem at the venous port on the dialysis catheter.

A more accurate way of assessing clotting within the dialyzer involves the measurement of the fiber bundle volume (FBV) or the residual volume within the blood compartment of the dialyzer. The FBV is easy to measure in vitro and has been the main criterion used to determine if a dialyzer is suitable for reuse in human dialysis units practicing reuse.[17] During the dialysis treatment, FBV may be measured to provide

Box 3
Signs of clotting in the extracorporeal circuit

Very dark blood

Dark streaks in the dialyzer

Foaming or clot formation in the venous trap

Clots at the arterial header

Increased arterial pressure with a decrease in venous pressure

    Clotting in arterial chamber or dialyzer

Increase in venous pressure

    Clotting in venous return

Decrease in fiber bundle volume

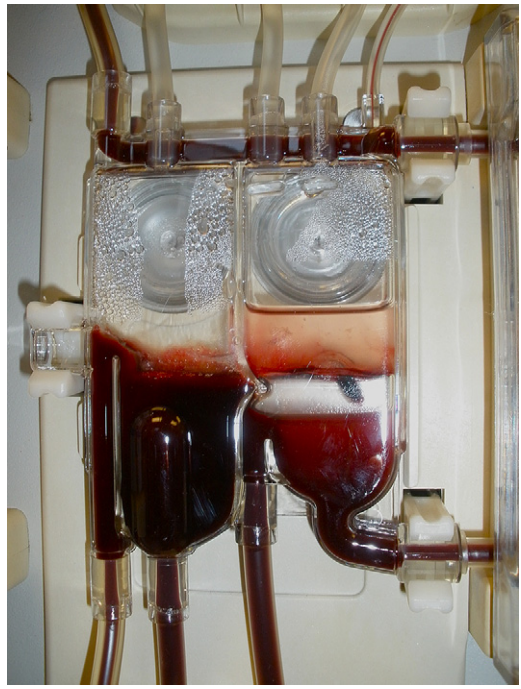

Fig. 1. Visual inspection of the arterial pressure chamber of this circuit reveals a fibrin clot that has formed at the blood-air interface. The blood level in the chamber has been lowered, and saline may be seen trapped above the clot.

a real-time assessment of dialyzer fiber clotting. Ultrasonic flow-dilution sensors are placed immediately predialyzer and immediately postdialyzer and connected to a hemodialysis monitoring system Transonic HD01 Hemodialysis Monitor (Transonic Systems Inc, Ithaca, NY, USA) and computer with appropriate software. There are 2 methods to measure FBV using this system. The first method is based on a bolus injection of saline and requires measurements from both sensors, whereas the second

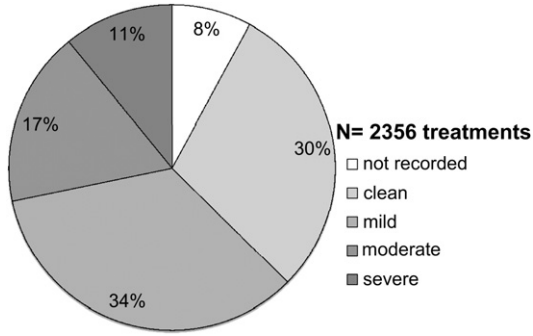

Fig. 2. Severity of clotting in hollow fiber dialyzers in 2356 intermittent hemodialysis treatments. Data were collected from 3 veterinary intermittent dialysis units in the United States (University of California Davis College of Veterinary Medicine, University of California Veterinary Medical Center – San Diego, and Animal Medical Center).

method is based on a step change in ultrafiltration and only requires the venous sensor. The obvious advantage of real-time assessment of clotting in the dialyzer is the ability to alter the dose of anticoagulant or stop the treatment before significant clotting and subsequent blood loss in the dialyzer.

HEPARIN

Unfractionated (UF) heparins include a family of highly sulfated polysaccharides composed of anionic glycosaminoglycans with molecular weights ranging from 4 to 40 kDa. UF heparin is by far the most frequently used anticoagulant for preventing thrombosis in the extracorporeal circuit in intermittent hemodialysis because of its low cost, relatively short biologic half-life, and ease of administration. UF heparin is highly negatively charged and binds nonspecifically to endothelium, platelets, macrophages, proteins, and some plastic surfaces. When given intravenously, UF heparin has a half-life of approximately 1.5 hours.[18] UF heparin has both hepatic and renal clearance and is also metabolized by the endothelium.

Heparin binds to antithrombin, causing a conformational change that results in activation.[19] Heparin-bound antithrombin inactivates multiple coagulation factors including thrombin and factor Xa and to a lesser degree factors VII, IXa, XIa, and XIIa. The binding of heparin may increase the rate of inactivation of these proteases by up to 1000-fold. Only UF heparin with more than 18 repeating saccharide units inhibits both thrombin and factor Xa, whereas shorter chains just inhibit factor Xa. Too much heparin may result in excessive bleeding, whereas inadequate administration leads to thrombosis in the extracorporeal circuit, with subsequent blood loss in the dialyzer and a decrease in the efficiency of the treatment.

In human medicine, the most important adverse effect of UF heparin administration is heparin-induced thrombocytopenia (HIT) syndrome. There are 2 documented syndromes of HIT. HIT type I is a transient reduction in platelet count, occurs in 10% to 20% of patients, and generally resolves within a few days. HIT type II involves an immune reaction and is typically a more serious condition. In the acute phase, there is a very high risk for both thrombocytopenia and thromboembolic disease. If left untreated, there is a more than 50% risk for the development of venous thrombosis within a month. In patients who develop HIT type II, use of all heparin-containing products must be discontinued and the patient must be systemically anticoagulated to prevent thrombosis. HIT type II has been reported in 3% to 12% of human patients who undergo hemodialysis.[20] Although there is a significantly lower risk for development of HIT syndrome with the exclusive use of low-molecular-weight heparins (LMWHs), once a patient develops HIT syndrome secondary to UF heparin, there is more than 90% cross-reactivity with LMWH.[21] Although this is by far the most significant obstacle to the use of UF heparin in human medicine, the HIT syndrome has not been recognized in veterinary medicine. Other adverse effects attributed to UF heparin include changes to lipid metabolism, alopecia, mild hyperkalemia, and osteoporosis.

MEASURING ANTICOAGULATION

The heparin dose and administration regime are an important part of the dialysis prescription. The unpredictable pharmacokinetics of UF heparin and its narrow therapeutic window make optimal dosing strategies difficult to define. Therefore, measuring the heparin concentration in the blood of a patient undergoing hemodialysis is ideal for inducing optimal anticoagulation. However, in clinical practice, it is not practical to measure blood levels of heparin directly; thus, the dose of heparin is managed by measuring its anticoagulant effect. The anticoagulant effect of heparin

is measured as the increased time taken for clot formation under controlled conditions. To be practical in the clinical setting of a dialysis unit, the clotting time assay must be inexpensive and convenient and, most importantly, it must provide rapid results at clinically relevant concentrations of heparin to allow for the adjustment of the heparin concentration during the dialysis treatment.

Both the activated partial thromboplastin time (aPTT) and activated clotting time (ACT) have been used to measure the anticoagulant effect of UF heparin in clinical practice. However, the aPTT seems to produce inconsistent results, especially at high blood levels of heparin required for adequate anticoagulation in extracorporeal therapies.[22] When using the aPTT to monitor UF heparin anticoagulation, it is recommended that a reagent-specific therapeutic range be established using heparin concentrations in blood.

The ACT is a point-of-care test that was first described in 1966 to screen for disorders of coagulation and as a tool for monitoring UF heparin therapy.[23] In this assay, whole blood is mixed with an activator of the extrinsic clotting cascade, and the time necessary for blood to congeal is measured. In the 1980s, use of the ACT to monitor UF heparin therapy gained clinical acceptance.[24–26]

For intermittent hemodialysis, the goal of anticoagulant therapy is to limit clotting in the dialyzer and circuit without causing excessive bleeding in the patient. To establish this goal, an ACT of 170 to 220 seconds has been recommended.[27] An alternative goal is an increase in ACT in the range of 140% to 180% of baseline. Increases of this magnitude in the ACT generally prevent visible clotting in the dialyzer and blood tubing.[28]

STANDARD HEPARIN PROTOCOL

In veterinary medicine, anticoagulation in routine intermittent hemodialysis typically consists of the systemic administration of a standard dose of heparin (10–50 U/kg) as a bolus 5 minutes before starting the dialysis treatment. Using frequent ACT monitoring (every 15–30 minutes), adequate anticoagulation is then maintained with a continuous infusion of heparin (10–50 U/kg/h) into the arterial limb of the circuit to maintain an ACT of 160 to 200 seconds (reference range: 90–140 seconds). Less commonly, boluses of heparin (10–50 U/kg) given every 30 minutes may be used in lieu of a constant rate infusion to achieve the same ACT goal or to more rapidly increase ACT in patients with a low ACT. The heparin infusion or bolus administration may be discontinued up to 30 minutes before the end of the treatment or continued throughout the treatment, depending on the patient's bleeding risk and the degree of clotting in the extracorporeal circuit. Careful observation of the patient and the extracorporeal circuit and careful ACT determinations ensure adequate systemic anticoagulation throughout the dialysis treatment (**Table 1**, **Fig. 3**).

Table 1
Suggested heparinization protocol for dogs and cats for intermittent hemodialysis

	Dogs	Cats
UF heparin bolus administered intravenously 5 min before initiating dialysis (U/kg)	25–50	10–25
Constant rate infusion of UF heparin during treatment	50–100 U/kg/h	20–50 U/cat/h
Target ACT during treatment (s)	160–180	150–180

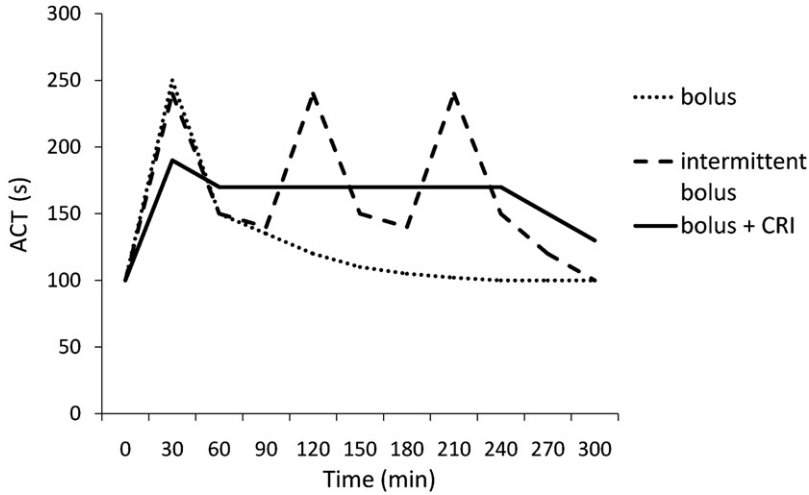

Fig. 3. Examples of anticoagulation profiles obtained from the administration of UF heparin during intermittent hemodialysis. The dotted line shows the prolongation of ACT obtained with a single loading dose of UF heparin. The dashed line shows the expected clotting time profile with intermittent bolus administration of heparin. The solid line shows the expected clotting time profile with an initial bolus followed by a CRI of UF heparin. In all these illustrations, heparin administration was discontinued 30 minutes before the end of the dialysis treatment. CRI, constant rate infusion.

STRATEGIES FOR HIGH-RISK PATIENTS

In some patients presented for hemodialysis, systemic anticoagulation may be contraindicated. Patients who have recently (<48 hours) undergone surgery, biopsy, or some other invasive procedure or patients with gastrointestinal hemorrhage, possible cranial trauma, pulmonary contusions, or any evidence of active bleeding should not receive systemic anticoagulation because of the risk of inducing or exacerbating bleeding. In these patients, alternate strategies must be used to prevent clotting in the extracorporeal circuit.

No-Heparin Hemodialysis

In human medicine, no-heparin hemodialysis is now the most common method of providing dialysis to patients at high risk of bleeding. This procedure was initially developed for use in patients with high bleeding risks.[29] The protocol for no-heparin hemodialysis requires pretreatment of the extracorporeal circuit with 2000 to 5000 units of UF heparin during the recirculation phase of preparation of the dialysis machine. Before beginning the dialysis treatment, the heparinized saline is flushed from the circuit with saline to prevent the patient from receiving a heparin bolus. Once the treatment is initiated, the blood flow rate is quickly increased to more than 300 mL/min and maintained at this rate for the duration of the treatment. Approximately every 15 to 30 minutes during the treatment, a saline bolus of 30 to 50 mL is flushed into the arterial side of the circuit. These boluses of saline help to wash fibrin strands through the dialyzer and into the venous pressure chamber, thus minimizing clotting. The volume status of the patient must be carefully monitored, and the volume of saline administered during the flushes must be removed via ultrafiltration, if necessary, to prevent hypervolemia. In addition, the arterial and venous pressures must be

monitored closely. If signs of early clotting are detected, the treatment should be stopped or switched to a low-dose heparin treatment to prevent more extensive clotting. No-heparin hemodialysis treatments have been used successfully in human medicine without a significant difference in treatment adequacy as compared with patients receiving standard anticoagulation therapy.[30] This method has also been used successfully in high-risk veterinary patients.

Heparin/Protamine Regional Anticoagulation

One of the first methods used to prevent coagulation in high-risk patients involved regional anticoagulation using heparin and protamine.[31] This method involves the constant infusion of UF heparin into the arterial limb of the extracorporeal circuit, with simultaneous infusion of protamine into the blood just before it is returned to the patient. The use of regional anticoagulation requires frequent checks of the ACT from the arterial and venous lines, with adjustments of the heparin and protamine infusion rates to maintain the ACT in the extracorporeal circuit at approximately 250 seconds and the ACT of the blood returning to the patient at the predialysis baseline.[32]

Protamine is a strongly basic low-molecular-weight protein that binds to and neutralizes the anticoagulant activity of UF heparin. Although precise dosing must be based on the results of clotting times, in general, 1 mg of protamine will antagonize 100 U of heparin. When protamine is used to counter the effects of heparin, there is a risk of rebound anticoagulation. This risk occurs because heparin is metabolized more slowly than protamine, thus free heparin is released from the protamine-heparin complex back into general circulation.[33] Compounding this effect is the fact that doses of heparin used in regional anticoagulation are typically higher than those used in routine heparin hemodialysis, thereby exacerbating the bleeding risk from rebound anticoagulation. Protamine may also cause dyspnea, bradycardia, and hypotension when administered rapidly. Because of the adverse effects described, the need for diligent monitoring, and the lack of proved benefit over other alternative methods of anticoagulation, regional heparinization is rarely used in routine practice.

Regional Citrate Anticoagulation

Another method of regional anticoagulation involves the continuous infusion of trisodium citrate solution into the arterial limb of the extracorporeal circuit.[34] Regional citrate anticoagulation has been shown to reduce the incidence of bleeding in high-risk patients compared with standard heparin protocols.[35] Citrate binds to ionized calcium in the blood and is a potent inhibitor of coagulation. The citrate-calcium complex is partially removed by the dialyzer. This removal is enhanced when calcium-free dialysate is used. To neutralize the effects of any remaining citrate, calcium chloride is infused into the venous return line. The citrate infusion rate is adjusted to keep the ACT at approximately 200 seconds in the arterial limb. Plasma calcium levels must be measured frequently and the calcium chloride infusion must be constantly adjusted accordingly to prevent hypocalcemia or hypercalcemia.

Another approach, proposed to minimize the amount of calcium infused and complications caused by a calcium-free dialysate, uses hypertonic trisodium citrate and a dialysate containing a calcium concentration of 3 mEq/L.[36] Complications associated with regional citrate anticoagulation are generally related to the patient calcium level, but metabolic acidosis because of the bicarbonate generated during citrate metabolism and hypernatremia from the citrate solution may occur as well. Careful monitoring of the electrolytes levels and acid-base status of the patient helps to prevent these complications.

ALTERNATE METHODS OF ANTICOAGULATION

In human medicine, UF heparin has been associated with significant adverse effects in some patients, most notably, HIT type II. In these cases, alternative strategies to prevent clotting in the extracorporeal circuit must be used.[37] Although some of these methods have been used extensively in human medicine, their use has not been reported in veterinary medicine. A brief description of some of the more common alternate methods of anticoagulation is outlined in the following sections. In general, these anticoagulants are significantly more expensive than UF heparin, thus limiting their use in veterinary medicine.

LMWH

LMWH has been used as an alternative to UF heparin for anticoagulation in hemodialysis.[38] LMWHs have average molecular weights ranging from 4 to 9 kDa and are produced from the controlled fractionation of heparin. Their smaller size produces more predictable pharmacokinetics, which makes their dosing simpler than UF heparin. LMWH binds antithrombin and inhibits factor Xa. The anticoagulant effect of LMWH can be monitored by determining the antifactor Xa activity in the patient's plasma.

LMWHs are expensive and have generally not been found to be superior to heparin in terms of dialysis-related bleeding or other complications.[39,40]

Direct Thrombin Inhibitors

Hirudins are polypeptides originally derived from the saliva of leeches. Hirudins act as potent direct thrombin inhibitors and do not require endogenous cofactors. Recombinant hirudins, such as lepirudin, have been investigated as anticoagulants for hemodialysis.[41] Typically, they are administered as a single dose at the beginning of the treatment. Use of hirudins in patients with kidney disease can be complicated because these substances are excreted via the kidneys and are not removed by conventional hemodialysis. In patients with renal disease, the half-life of hirudins may be significantly prolonged, sometimes for days. Hirudins are seldom used in clinical practice because of the significant risk of bleeding.

Synthetic thrombin inhibitors, such as argatroban, have been investigated as an alternative to heparin for anticoagulation during dialysis. Argatroban is metabolized in the liver and therefore may be used in patients with significant kidney disease, with some dose adjustment. With careful monitoring, argatroban has been used in dialysis of human patients who are intolerant to UF heparin due to HIT syndrome. Argatroban has been shown to provide acceptable anticoagulation with tolerable side effects.[42]

Prostacyclin Anticoagulation

Prostacyclin is a vasodilator and potent inhibitor of platelet aggregation.[43] Prostacyclin is administered as a continuous infusion into the arterial limb of the extracorporeal circuit to prevent clotting. It has a relatively short half-life (approximately 4 minutes) and is rapidly metabolized by the endothelium, allowing for rapid adjustment of dose and tight control of coagulation. Hypotension from vasodilatation is a common and often serious side effect. In addition, human patients often report headache and dizziness. Because these side effects limit the clinical usage of prostacyclin, current efforts are directed toward the development of analogues without the hypotensive effects.

SUMMARY

Several methods to prevent extracorporeal circuit clotting during hemodialysis have been used in human medicine. UF heparin remains the mainstay of anticoagulant therapy in both human and veterinary intermittent hemodialysis. Different UF heparin regimes may be used depending on the bleeding risk of the patient. In patients with active bleeding or with a recent history of surgery or hemorrhagic episodes, hemodialysis may be performed without any anticoagulation or with regional anticoagulation.

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