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Past, present, and future perspectives of heparins in clinical settings and the role of impaired renal function

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Future perspectives

ABSTRACT

Heparin, whose discovery goes back one hundred years, was first detected as a thromboplastin from liver tissue, and its anticoagulant action was only identified later. The procoagulant action of heparin, which was later characterized as an immunologic reaction by binding to platelet-factor IV, presenting as heparin-induced thrombocytopenia, remains as a side effect. For more than 60 years heparin has been the immediate anticoagulant of choice in many clinical indications. Further development of heparins resulted in the production of low-molecular weight heparins and Fondaparinux, which substituted heparin for many indications and has received many more new indications, including administration for non-anticoagulant purposes. This development is still ongoing and has resulted in more than 300 registered clinical trials at the end of 2015. All types of heparins are still investigated in patients with impairment of renal function to improve the safety of treatment. New therapeutic strategies for the prevention and treatment of thromboembolism, as well as of the non-anticoagulant actions of natural and modified types of heparins, are studied intensively. The clinical study designs include treatment with vitamin-K and non-vitamin K oral anticoagulants. Consequently, heparins, low-molecular weight heparins and Fondaparinux play an important role in the human health care system.

1. Past

Heparin was first described by Howell and McLean when they studied a thromboplastin, a procoagulant substance from the brain and later from liver ([1], review). Jay McLean was aware of several research results from Germany reporting peptones from organs acting as thromboplastin [2]. During 1915 and 1916, working in the laboratory of WH Howell, he purified an agent from heparphosphatide, which contaminated the cephalins obtained also from other brain and heart tissues, without telling Howell the results [3]. When Howell became aware of the data of his student he went on to analyse the contaminated cephalin himself and identified anticoagulants, naming them antithrombin and heparin [4]. Two batches of the purified compound were injected intravenously into dogs to demonstrate the anticoagulant heparin inhibition of blood coagulation [5].

Reports on the prevention of postoperative venous thromboembolism date back to the end of the 1930s. Crafoord et al reported the first prophylactic uses of repeated intravenous injections of heparin in postoperative medicine and in perinatal gynaecology [6]. Bauer described the efficacy of heparin injection by reducing the incidence of mortality to 1–4% in 16,495 patients between 1939 and 1945, compared to 18% without heparin observed between 1929 and 1938, at the Mariestad hospital in Sweden. A reduction of fatal pulmonary embolism (PE) was found from 47 of about 25,000 cases to 3 of about 16,000 cases ([7], reviewed in [1]).

Lessons from history:

Heparin is standard of care for treatment of acute PE and DVT
Heparin is standard of care for postoperative prophylaxis of VTE
Vitamin K antagonists are effective for prevention for recurrent VTE

2. Present

Today, UFH and LMWHs are known to effectively prevent thromboembolism in many indications including extracorporeal circulation with UFH and haemodialysis with UFH and LMWHs. LMWHs are more effective for the prevention of recurrent events of venous thromboembolism (VTE) for several months in patients with malignant disease compared to vitamin K antagonist (VKA). Heparins are administered by intravenous or subcutaneous applications and UFH requires laboratory adjustment to maintain the activated partial thromboplastin time (aPTT) within a therapeutic range of 1.5- to 2.5-fold prolongation – subcutaneous administration may be provided at fixed doses for treatment of acute VTE. UFH and LMWHs require the repeated determination of platelet count due to the development of type I or type II heparin-induced thrombocytopenia (HIT) [8]. LMWHs improve anticoagulant therapy compared to UFH in many indications as a result of adjustment for

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body weight, or when using fixed dosing, and exhibit side effects less frequently. Other limitations for both groups of heparins are any kind of haemorrhage, cutaneous allergic reactions, heparin-induced skin necrosis, decreased antithrombin levels, heparin-resistance, hair loss, increases in liver enzyme levels, thrombotic occlusions in any organ as presentation of HIT type II, and other side effects all of them occuring less frequently with LMWHs compared to UFH [9,10].

Fondaparinux is a synthetic pentasaccharide with high affinity to antithrombin and an elimination half-life of about 17 hrs following subcutaneous administration. Its efficacy and safety are similar or better than for LMWHs in several indications. It does not bind to platelet factor 4 (PF4) as UFH and LMWHs, which form a complex between UFH, or LWMHs with a PF4 tetramer, generating heparin-PF4 antibodies. Only a few cases of HIT have been reported during therapy with Fondaparinux. In fact, Fondaparinux is used for patients with HIT and cutaneous allergic reactions to heparins to allow anticoagulation to be continued. Owing to its low molecular weight, Fondaparinux is mainly excreted by glomerular filtration and the elimination half-life is prolonged by decreased renal function. Other side effects relate to bleeding complications, which occur less frequently compared to LMWHs [11]. Fondaparinux is administered at fixed doses or adjusted for body weight classes in VTE treatment without laboratory-guided dose adjustment according to anti-factor Xa levels. Requirement of specific laboratory methods and systemic administration remain as limitations for therapy [12].

Lessons from use of heparins

Heparin has to be administered at a dose prolonging aPTT 1.5- to 2.5-fold
LMWHs are almost as effective and safe as heparin
Incidence of HIT less frequent with LMWH compared to UFH
Body weight adjustment of LMWHs dosage are well established
Fondaparinux is almost as effective and safe as LMWHs
HIT does not occur with fondaparinux only

3. Relevance of impaired renal function

The relevance of intact renal function for heparins increased with the development of different LMWHs and Fondaparinux (reviewed in [13]). Early reports described the elimination of heparins by as much as 30% as inactive desulfated compound. Elimination of sulfated polysaccharides such as heparins occurs through kidneys, the elimination being higher with decreasing molecular weight and also for the pentasaccharide Fondaparinux. For two of the LMWHs, comparative studies supported this hypothesis. Tinzaparin, with a higher molecular weight was excreted almost independently of the degree of renal function, in contrast to Enoxaparin with a lower mean molecular weight, which is excreted as a function of renal function. It is also reported that lowering the degree of sulfation of a polysaccharide renders renal elimination less important [13]. As the absolute number of negative charges per oligosaccharide may be independent of the molecular weight, it remains open which of the two characteristics influence renal elimination. This is, however, not important for clinical administration, because for Enoxaparin a 50% reduction of dose is required at a creatinine clearance (CrCl) of <30 ml/min and Fondaparinux is contraindicated at this stage of reduced renal function. Clearance of Enoxaparin has been described as a function of renal elimination and of lean body weight. This was supported by findings that higher anti-factor Xa activity was maintained longer if subjects had been dosed according to anti-factor Xa levels compared to conventional fixed dosing [14].

In the RIETE Registry (Registro Informatizado de la Enfermedad TromboEmbólica) multivariate analysis indicated that patients were at increased risk for all-cause death (odds ratio, 1.8) and fatal pulmonary embolism (odds ratio, 2.3) when treated initially with UFH for acute VTE compared to LMWH [15]. A relation to renal function was not reported.

The main disadvantage for elimination of heparins by impairment of renal function is the accumulation of the anticoagulant with an increased risk of bleeding complications. A meta-analysis confirmed the increased risk of bleeding for patients with renal insufficiency receiving LMWHs [16]. Twelve studies including almost 5000 patients found major bleeding in 5% of patients with CrCl <30 ml/min, compared to 2.4% in patients with CrCl >30 ml/min (odds ratio = 2.2, p = 0.013). The rate of major bleeding decreased with Enoxaparin dose reduction, either empirically or based upon anti-Xa monitoring. There were insufficient data to determine bleeding rates with Tinzaparin and Dalteparin. In the ExTRACT-TIMI 25 trial, the Enoxaparin dose was reduced for age ≥75 years (0.75 mg/kg SC BID) and with CrCl <30 ml/min (1 mg/kg once daily). Patients with CrCl <30 ml/min still demonstrated a trend towards more major bleeding despite the reduced Enoxaparin dose. Several additional studies in patients with acute coronary syndrome added that, despite reducing the dose of Enoxaparin by 50% at an age >75 years and a CrCl of 15 to 30 ml/min, this did not reduce the incidence of major bleeding compared to conventional dosing. In contrast, lowering the dose to less than 0.5 IU/ml as peak levels increased the 30-day mortality. Controversially, elevated anti-Xa levels did not predict major bleeding. Not all LMWH products are the same in regards to reliance upon renal elimination. Available data are not sufficient to support these conclusions for Tinzaparin and Dalteparin. In contrast, UFH does not rely on renal elimination and remains an option for treatment in patients with CrCl <30 ml/min [12,17,18].

LMWHs have been shown to be effective for anticoagulation in chronic intermittent haemodialysis [13]. The advantages of LMWH over UFH are a lower incidence of bleeding risk, lower incidence of thrombocytopenia, and improvement of hypertriglyceridemia [19]. Patients on chronic intermittent haemodialysis often suffer from an increased bleeding risk. In these patients LMWH may be beneficial [20]. Dalteparin, Enoxaparin, Certoparin and Nadroparin [21] are approved for anticoagulation in haemodialysis. Dosing differs among the LMWHs as well as the anti-factor Xa levels to be obtained during or at the end of dialysis. In contrast to UFH, nadroparin required no laboratory monitoring of anticoagulant activity owing to the reliable anticoagulant response following its administration. Compared with UFH, Nadroparin was beneficial in terms of lipid and possibly bone parameters. Nadroparin administered by a bolus dose, followed by a continuous infusion was also shown to be effective and safe in patients undergoing continuous renal replacement therapy for acute renal failure [21]. In the IRIS trial (Innohep in Renal Insufficiency Study) no significant accumulation was detected with age, bodyweight or creatinine clearance comparing Tinzaparin versus UFH [22]. The mean anti-Xa activity did not differ significantly between the patients who experienced clinically relevant bleeding and those who did not. The high proportion of high molecular weight moieties in Tinzaparin may account for its reduced dependence on renal elimination [23].

The influence of impairment of renal function on UFH and LMWH (Nadroparin) levels in plasma and urine was investigated in a small study at our centre in patients on chronic haemodialysis. Following a bolus of 5,000 IU UFH, all samples were taken at the end of dialysis after 4 hrs. The anti-factor Xa (aXa) activity of UFH in plasma and urine was determined using Coamatic assay (Instrumentation Laboratories, Kirchheim, Germany). The results showed that the expected plasma anti-factor Xa levels and activity of heparin in urine was below the detection limit of the assay. Heparin plasma levels did not correlate with creatinine clearance (CrCl) (Table 1).

Patients with renal impairment, but not on haemodialysis or LMWH received 36 mg Nadroparin once daily subcutaneously in the morning. Blood and urine samples were taken after 4 hours. The anti-factor Xa activity in plasma was about 0.17 IU/ml as expected (Table 2). The amount of Nadroparin present in the urine was below the detection limit of the method. The plasma concentration did