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Use of fondaparinux as an anticoagulant during hemodialysis: a preliminary study

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fondaparinux – arixtra – hemodialysis – high-flux

Abstract. Objective: To study the effect of fondaparinux, a new antithrombotic agent, as an anticoagulant during a 4-hour conventional hemodialysis session. Materials and methods: Fondaparinux was administered as an anticoagulant to 16 chronic hemodialysis patients during a single 4-hour hemodialysis session at an intravenous bolus dose of 2.5 mg. Eight patients were using high-flux polyester polymer alloy (PEPA) dialyzers (Group A) and the remainder low-flux polysulfone dialyzers (Group B), whilst all had received conventional doses of tinzaparin sodium as an anticoagulant during the previous month. The dialyzers were primed with 1 l of normal saline containing 5,000 IU of unfractionated heparin. Blood samples for the measurement of INR, APTT (activated partial thromboplastin time) and anti-Xa levels were taken before the study dialysis session (pre), 5 min postdialysis (post), and before the next dialysis session (next). Mean fibrin/clot formation in the extracorporeal circuit and dialyzer was assessed macroscopically by visual inspection and was graded using a 4-point scale. Results: Predialysis anti-Xa levels were 0.04 ± 0.03 IU/ml in Group A, and 0.025 ± 0.025 IU/ml in Group B (p = NS). Postdialysis anti-Xa levels were significantly higher than predialysis levels in both groups (Group A = 0.16 ± 0.04 IU/ml, Group B = 0.46 ± 0.12 IU/ml, p < 0.02 for both) and significantly higher in Group B compared to Group A (p ≤ 0.025). Anti-Xa levels before the next dialysis session were 0.06 ± 0.04 IU/ml in Group A and 0.25 ± 0.06 IU/ml in Group B (p < 0.0001 between Groups A and B). APTT values were significantly higher in postdialysis than predialysis samples for both groups (higher by 27.0 ± 26.0% in Group A and 24.3 ± 31.9% in Group B). No significant differences were found when comparing APTT values in pre, post and next samples between Groups A and B. No differences were also found between pre, post and next samples for INR values, either within or between groups. Mean fibrin/clot formation score in the extracorporeal circuit at the end of the study dialysis session was significantly higher in patients of Group A than those of Group B (p < 0.05). Dialysis had to be terminated before the completion of 4 hours in 2 patients of Group A because of the presence of extensive fibrin/clots in the circuit and dialyzer. Conclusions: Our findings indicate that fondaparinux sodium at an intravenous dose of 2.5 mg can be used successfully as an anticoagulant during a 4-hour conventional hemodialysis session in patients dialyzed with low-flux polysulfone dialyzers, but not in those dialyzed with high-flux dialyzers. However, anti-Xa levels in the former patients were still increased before the next dialysis session, potentially exposing the patients to an increased risk of bleeding.

Introduction

Low-molecular weight heparins (LMWHs) are fragments of conventional porcine-derived heparin that were developed in an effort to provide more selective inhibition of enzymatic function and to lower the adverse effects associated with the use of heparin [Christidou et al. 2005]. Fragmentation of heparin creates products that maintain activity against factor Xa and release antithrombotic factors, but these products have significantly less activity against factor IIa [Hirsh et al. 2001]. Treatment with LMWHs, therefore, provides antithrombotic effects with a lower anticoagulant effect and may reduce the risk of bleeding. Although the cost of LMWHs in comparison to unfractionated heparin is higher, they are the preferred anticoagulant during hemodialysis, in some centers [Lai et al. 1996]. Fondaparinux sodium (Arixtra) is the first of a new class of antithrombotic agents that bind to antithrombin and inhibit the action of factor Xa [Reynolds et al. 2004]. It is a synthetic pentasaccharide that inhibits only factor Xa and does not directly inhibit thrombin (activated factor II) [Internet 2006].

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Moreover, it does not have any effect on platelets and has been used as an anticoagulant in patients with heparin-induced thrombocytopenia syndrome (HIT II syndrome) [Girolami and Girolami 2006], although this has recently been disputed [Warkentin et al. 2007]. Although it is eliminated by the kidneys and has a rather long half-life, for all the above reasons, it seems to be a reasonable candidate for use as an anticoagulant during conventional hemodialysis. Since there are no data in the literature concerning its use on this topic, we undertook the present study.

Materials and methods

A total of 16 stable chronic hemodialysis patients, comprising 6 females and 10 males with a median age of 68 years (range 32 – 82), participated in the study after giving their informed consent. They were undergoing 4-hour bicarbonate hemodialysis 3 times per week, for a median period of 57.5 months (range 12 – 185). The causes of renal disease were chronic glomerulonephritis in 4 patients, diabetic nephropathy in 2, hypertensive nephrosclerosis in 2, polycystic kidneys in 1, interstitial nephritis in 1, and unknown in the remaining 6 patients. None of the patients had significant residual renal function (urine output were < 100 – 150 ml/day). All patients had well-functioning vascular accesses (15 arteriovenous fistulae and one synthetic graft) and no patient was receiving antiplatelet agents, aspirin or coumarin. The patients were divided into Groups A and B according to the dialyzers they used. 8 patients (Group A) were receiving hemodialysis using high-flux polyester-polymer alloy (PEPA) dialyzers (FDX-18GW, surface area 1.8 m^2, Nikkiso Co., Tokyo, Japan), while the remaining 8 patients (Group B) were using low-flux polysulfone dialyzers (ULF 18, surface area 1.8 m^2, Bio-implant GmbH, Hamburg, Fresenius Medical Care, Germany). During the study dialysis session, blood flow rate was set to 300 ml/min, dialysate flow rate to 600 ml/min, and the dialysis time to 240 min. Dialyzers were primed with 1 l of normal saline containing 5,000 IU of conventional unfractionated heparin. For the last month, all patients were receiving tinzaparin sodium (Innohep) as an anticoagulant at a dose of 50 – 75 IU/kg. At the beginning of the study dialysis session, which was the morning midweek dialysis session (Wednesday or Thursday), and after the priming of dialyzers, 2.5 mg of fondaparinux sodium (Arixtra, GlaxoSmithKline (GSK), Brentford, Middlesex, UK) was administered as an intravenous bolus injection for anticoagulation.

An arterial fistula needle was used to take blood samples in every patient before the hemodialysis session (sample "pre"), 5 min after the end of the hemodialysis session (sample "post"), and before the next hemodialysis session (sample "next"). Hemoglobin (Hb), prothrombin time (PT) and INR, activated partial thromboplastin time (APTT), and anti-Xa factor activity were measured in pre, post and next samples, while BUN levels were measured in pre and post samples for Kt/V (Daugirdas II) calculation [Daugirdas 1993].

BUN and hemoglobin were determined by conventional laboratory methods. PT-INR and APTT were measured using the ACL TOP system (Instrumentation Laboratory, Lexington, MA, USA) and the reagents PT fibrinogen recombinant and APTT SP (Instrumentation Laboratory), respectively. The standard APTT was the same for all measurements (30 seconds). For the estimation of fondaparinux activity in our study, we measured anti-Xa levels in order to obtain a comparative element with well-known LMWH activity. Anti-Xa levels were measured via a STA compact using a colorimetric assay of low-molecular weight heparins (STA-Rocachrom HBPM/LMWH, Diagnostics Stago, Asnieres-sur-Seine, France).

In an additional analysis, the fondaparinux half-life between hemodialysis sessions was estimated as $t_{1/2} = 0.693 \times (t_{next} - t_{post})/ \ln (\text{anti-Xa}_{post}/\text{anti-Xa}_{next})$, where $t_{next} - t_{post}$ is the time between the dialysis sessions and ln represents the natural logarithm. This calculation assumes linear 1-compartment pharmacokinetics, absence of a concentration rebound after hemodialysis (which is reasonable since it appears that fondaparinux does not distribute into tissues) and a linear relationship between fondaparinux concentrations and measured anti-Xa activity.

In order to quantitatively assess the efficacy of anticoagulation on the extracorporeal

Table 1. Demographic data of patients.

Data	Group A	Group B	p values (comparing Group A to B)
Age (years)	62.6 ± 14.8	62.1 ± 16.1	NS
Gender	4F, 4M	2F, 6M	NS
HD (months)	72.0 ± 30.6	68.8 ± 64.4	NS
BW_{pre} (kg)[a]	76.4 ± 19.7	73.8 ± 6.8	NS
BW_{post} (kg)	73.9 ± 19.2	71.5 ± 7.0	NS
ΔBW (kg)	2.5 ± 0.6	2.2 ± 0.7	NS

HD = Hemodialysis, BW = Body Weight, ΔBW = Difference between BW_{pre} and BW_{post} of the study dialysis. [a]In both groups, BW_{pre} was significantly higher than BW_{post} ($p < 0.0001$).

Table 2. Mean BUN, Kt/V and fibrin/clot values during the study dialysis.

Parameters	Group A (n = 8)	Group B (n = 8)	p values (comparing Group A to B)
Fibrin/clot score (1st hour)	0.12 ± 0.35	0.12 ± 0.35	NS
Fibrin/clot score (2nd hour)	0.62 ± 0.51	0.62 ± 0.51	NS
Fibrin/clot score (3rd hour)	1.12 ± 0.64	0.87 ± 0.35	NS
Fibrin/clot score (end of the study dialysis)[a]	1.62 ± 0.91	0.87 ± 0.35	< 0.05
BUN_{pre} (mg/dl)[b]	68.5 ± 17.0	72.1 ± 11.4	NS
BUN_{post} (mg/dl)	23.0 ± 6.2	28.7 ± 10.4	NS
Kt/V (Daugirdas II)	1.27 ± 0.29	1.11 ± 0.21	NS

[a]Fibrin/clot scores within both groups were significantly higher at the 3rd hour and at the end of the dialysis session than at the end of the 1st hour ($p < 0.01$ for both). The fibrin/clot score in Group A at the end of dialysis was also significantly higher than the score at the end of the 2nd hour ($p < 0.01$). [b]BUN_{pre} was significantly higher than BUN_{post} within both groups ($p < 0.0001$).

circuit, the degree of fibrin/clot formation in the dialyzer and the venous drip chamber was subjectively graded using a 4-point scale, with zero indicating no fibrin/clot formation, and 3 indicating total occlusion. The macroscopic visual inspection assessment was carried out by one of the researchers and the responsible nurse, every hour for the first 3 hours and at the end of each dialysis session after the blood returned to the patient and the circuit had been flushed with normal saline. Any episode of significant thrombosis or hemorrhage occurring during or between the study dialysis session and the next session was also recorded.

The unpaired and the paired Student's t-test were used for statistical analysis of independent and dependent variables, respectively. The Fisher's exact test was used for comparison of categorical variables. A probability of $p < 0.05$ was considered significant. Data are expressed as means ± SD. The timing of blood sample withdrawal (pre, post and next) had been added to the end of the abbreviated parameter name as an index to facilitate data interpretation.

Results

Table 1 shows the demographic data of patients in Groups A and B, while mean BUN values pre- and 5 min postdialysis, calculated Kt/V and hourly fibrin/clot scores are shown in Table 2. In both groups, BUN_{pre} was significantly higher than BUN_{post} ($p < 0.0001$ for both). Moreover, fibrin/clot scores for both groups were significantly higher at the 3rd hour and at the end of dialysis than at the end of the 1st hour ($p < 0.03$ for both groups and for both comparisons). In Group A, the fibrin/clot score at the end of dialysis was higher than the score at the end of the 2nd hour ($p < 0.03$). The extracorporeal circuit possessed extensive clotting after 3.5 hours in 2 patients of Group A and the session had to be interrupted 22 and 26 min before the programmed end. Table 3 shows Hb, INR, APTT and anti-Xa factor values before the study dialysis session, postdialysis and before the next dialysis. In both groups, no significant differences were found between INR values when pre, post and next samples were compared. Additionally, no significant differences were found in either group when APTT values were compared between pre and next samples. Postdialysis APTT values were significantly higher than predialysis values in Groups A and B ($p < 0.02$ for both). The percentage differences were 27 ± 26.0% in Group A and 24.3 ± 31.9% in Group B. No significant differences were found between Groups A and B when INR and APTT values were compared in pre, post and next samples.

Anti-Xa levels before the study dialysis session (anti-Xa_{pre}) did not differ between Groups A and B. However, anti-Xa_{post} and

Table 3. Hematological parameters (Hb, INR, APTT, anti-Xa) before the study dialysis (pre), after the end of dialysis (post) and before the next dialysis (next).

Hematological parameters	Group A (n = 8)	Group B (n = 8)	p values (comparing Group A to B)
anti-Xa_{pre} IU/ml	0.04 ± 0.03	0.025 ± 0.02	NS
anti-Xa_{post} IU/ml[a]	0.16 ± 0.04	0.46 ± 0.11	< 0.0001
anti-Xa_{next} IU/ml[b]	0.06 ± 0.04	0.25 ± 0.06	< 0.0001
$APTT_{pre}$ (sec)	27.6 ± 1.35	31.8 ± 7.4	NS
$APTT_{post}$ (sec)[c]	34.8 ± 7.8	38.7 ± 9.2	NS
$APTT_{next}$ (sec)	27.6 ± 3.8	32.3 ± 5.2	NS
INR_{pre}	0.87 ± 0.04	0.88 ± 0.06	NS
INR_{post}	0.86 ± 0.07	0.88 ± 0.09	NS
INR_{next}	0.88 ± 0.03	0.94 ± 0.15	NS
Hb_{pre} g/dl	11.7 ± 1.1	11.9 ± 0.8	NS
Hb_{post} g/dl[d]	12.6 ± 1.4	12.6 ± 0.9	NS
Hb_{next} g/dl	11.5 ± 0.8	12.0 ± 0.7	NS

[a]anti-Xa_{post} was statistically higher than anti-Xa_{pre} or anti-Xa_{next} within both groups ($p < 0.01$ for both parameters in both groups).
[b]anti-Xa_{next} in Group A did not differ significantly from anti-Xa_{pre}. In Group B, anti-Xa_{next} was significantly higher than anti-Xa_{pre} ($p < 0.001$).
[c]$APTT_{post}$ was statistically higher than $APTT_{pre}$ or $APTT_{next}$ within both groups (for both parameters, $p < 0.03$ in Group A and $p < 0.04$ in Group B).
[d]Hb_{post} was statistically higher than Hb_{pre} or Hb_{next} within both groups ($p < 0.02$ for both parameters in both groups).

anti-Xa_{next} levels in Group B patients were significantly higher than corresponding levels in Group A patients ($p < 0.001$ for both parameters). Anti-Xa_{post} levels were statistically higher than anti-Xa_{pre} and anti-Xa_{next} levels in both groups ($p < 0.02$ for both parameters in both groups). In Group A, anti-Xa_{next} levels did not differ significantly from anti-Xa_{pre} levels. However, anti-Xa_{next} levels in Group B were significantly higher than anti-Xa_{pre} levels ($p < 0.02$). Median fondaparinux half-life between hemodialysis sessions was 18.9 hours (–68.8 – 57.3) in Group A and 52.5 hours (34.8 – 76.9) in Group B ($p = 0.06$).

Discussion

Fondaparinux sodium (Arixtra) is an antithrombotic agent inhibiting only factor Xa. It is a synthetic pentasaccharide that does not directly inhibit thrombin (activated factor II). LMWHs inhibit factors Xa and IIa. The antithrombotic activity of fondaparinux sodium is the result of antithrombin III- (ATIII) mediated selective inhibition of factor Xa and in individuals with normal renal function it is eliminated in urine mainly as an unchanged drug [Bauer 2006, Reynolds et al. 2004]. Thus, elimination is expected to be prolonged in patients with renal impairment since the major route of elimination is urinary excretion. It possesses a molecular weight of 1,728 Da and a half-life of 17 to 21 hours [Bauer 2006].

There is no information in the literature regarding the use of fondaparinux as an anticoagulant during hemodialysis. However, there are two case reports concerning fondaparinux use during hemodialysis in 2 patients with end-stage renal disease [Haase et al. 2005, Sharathkumar et al. 2007]. In this preliminary study, we intravenously administered 2.5 mg of fondaparinux as an anticoagulant in patients undergoing chronic intermittent hemodialysis. Since the anti-Xa activity of fondaparinux increases with increasing drug concentration, reaching maximum values in approximately 3 hours after subcutaneous administration, we thought that it could be used as an anticoagulant during a 4-hour conventional hemodialysis session.

Our study shows that fondaparinux at a dose of 2.5 mg can be used as an anticoagulant only in patients using low-flux polysulfone dialyzers. In contrast, its use in hemodialysis with high-flux (PEPA) dialyzers (Group A patients) revealed an increased risk of extracorporeal circuit and dialyzer thrombosis. In 2 patients, hemodialysis had to be interrupted 22 and 26 min before the completion of the 4-hour session because of extensive clotting of the dialysis circuit. This can be attributed to an increased removal of fondaparinux during dialysis with high-flux membranes and a subsequent inadequate anticoagulation effect. It has been reported that neither UFHs nor LMWHs cross the dialyzer membrane in any measurable quantity, due to their relatively large size [Amanzadeh and Reilly 2006]. However, 1 study of high-flux membranes showed reduced anti-factor Xa levels immediately and 4 hours after administration of enoxaparin in comparison with low-flux membranes. This indicated that high-flux membranes might require greater doses of enoxaparin to ensure adequate anti-

coagulation during dialysis [McMahon et al. 2004]. Elimination of enoxaparin by high-flux hemodialysis membranes has been documented during CRRT [Isla et al. 2005].

The results of our study are in agreement with these findings. It should be noted that fondaparinux has a much smaller molecular weight compared to other LMWHs used during conventional hemodialysis and, thus, might be eliminated through the high-flux dialyzers more effectively.

Although the number of patients studied was rather small and the fibrin/clot assessment subjective, we found statistically significant differences when comparing the mean fibrin/clot score between high-flux and low-flux dialyzers at the end of the study dialysis session. This finding, along with the very low anti-Xa levels postdialysis in patients of Group A and the development of extensive clotting of the extracorporeal circuit in 2 patients of this group, indicate that fondaparinux is not applicable as an anticoagulant at a dose of 2.5 mg in such patients. The anti-Xa level postdialysis in Group A patients was 0.16 ± 0.01 IU/ml, and is significantly lower than the 0.40 IU/ml level considered the cut-off point for antithrombotic activity of LMWHs at the end of hemodialysis [Grau et al. 1992, Guillet et al. 2003]. As a consequence, the anti-Xa levels before the next dialysis were very low (0.06 ± 0.01 IU/ml) and did not differ from levels measured before the study dialysis session. In contrast, the mean anti-Xa level postdialysis in patients of Group B was 0.46 ± 0.11 IU/ml, well above the limit of 0.40 IU/ml. Moreover, anti-Xa levels in these patients before the next dialysis session (44 hours later) were 0.25 ± 0.05 IU/ml, being significantly higher ($p < 0.0001$) than corresponding levels in Group A patients. These high anti-Xa levels in Group B patients before the next dialysis session are in concordance with the adequate postdialysis anti-Xa levels in these patients and the long elimination half-life of the drug, especially in the presence of renal failure. According to Guillet et al. [2003], as well as our published [Christidou et al. 2005] and unpublished data (personal observations), predialysis anti-Xa levels in patients undergoing thrice-weekly hemodialysis using LMWHs as anticoagulants are usually equal to or lower than 0.10 IU/mg. All of the above indicate a higher removal rate of fondaparinux during high-flux dialysis compared to low-flux dialysis.

Moreover, it should be noted that besides anticoagulation, the extracorporeal circuit and dialyzer thrombogenicity are also dependent on many other factors such as blood flow rate, blood viscosity, dialyzer membrane material, etc. Although low-flux polysulfone and high-flux PEPA membranes are both synthetic and biocompatible membranes, high-flux membranes are more hydrophobic and exhibit a higher adsorption and elimination of proteins, factors that could increase thrombogenicity [Matata et al. 1996].

In conclusion, our study shows that fondaparinux administered intravenously at a dose of 2.5 mg can be used successfully as an anticoagulant during a 4-hour conventional hemodialysis session in patients dialyzed with low-flux polysulfone dialyzers, but not in those dialyzed with high-flux dialyzers. However, anti-Xa levels in the former patients were still increased before the next dialysis session. This might expose the patients to an increased bleeding risk. Furthermore, drug accumulation might occur after repeated administration of fondaparinux in patients using low-flux membranes. More studies are needed to determine the safe use and dose of fondaparinux as an anticoagulant during conventional hemodialysis. Such studies should evaluate the concentration course during and between hemodialysis sessions, preferably including high-flux membranes other than PEPA.

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