Use of the pentasaccharide fondaparinux as an anticoagulant during haemodialysis

Robert M. Kalicki[1], Fabienne Aregger[1], Lorenzo Alberio[2], Bernhard Lämmle[2], Felix J. Frey[1], Dominik E. Uehlinger[1]

[1]Department of Nephrology and Hypertension, Inselspital, University of Bern, Switzerland; [2] Division of Haematology and Central Haematology Laboratory, Inselspital, University of Bern, Switzerland

Summary

No data about the use of the pentasaccharide fondaparinux, a highly selective indirect inhibitor of factor Xa, in patients treated with haemodialysis are available. Therefore, we investigated the pharmacokinetics and -dynamics of fondaparinux in 12 patients during haemodialysis. The anti-Xa activity (expressed as fondaparinux equivalent) was monitored, a semiquantitative clotting scale (SQCS) ranging from 0 (no visible traces of coagula) to 3 (complete clotting of the dialysis circuit) was applied, and the digital compression time necessary to achieve haemostasis at the puncture site was determined. After an initial period, when the regular heparin dose was replaced once weekly by fondaparinux, 0.05 mg/kg, the pentasaccharide was administered for nine consecutive haemodialysis sessions. Peak anti-Xa activity increased from 0.61 ± 0.14 μg/l after the first dose to 0.89 ± 0.24 μg/l after dose 9 (P<0.001), whereas predialysis anti-Xa activity steadily rose to 0.32 ± 0.09 μg/l (P<0.001). A sufficient but slightly less effective anticoagulation with a mean SQCS of 1.19 ± 0.71 (n=121) was obtained by fondaparinux as compared with 0.65 ± 0.58 (n=60, P<0.005) by 4,825 ± 1,703 U of unfractionated heparin. Mean digital compression time rose slightly during fondaparinux from 23.7 ± 7.4 minutes to 24.8 ± 7.5 minutes (P<0.05) and, more important, six of the 12 patients reported minor bleeding problems during the interdialytic interval. Thus, fondaparinux can be used to prevent circuit clotting during haemodialysis; however, accumulation results in an interdialytic increase of anti-Xa activity. Therefore, fondaparinux should be reserved for patients requiring systemic anticoagulation on the days off dialysis.

Keywords

Dialysis, anticoagulation, pentasaccharide, fondaparinux, anti-Xa

Thromb Haemost 2007; 98: 1200–1207

Introduction

Despite constant improvements in dialysis membrane characteristics, increased biocompatibility and reduced thrombogenicity, anticoagulation remains necessary during haemodialysis procedures in order to prevent clotting of the dialyzer and/or extracorporeal circuit and reduce the systemic procoagulatory state (1, 2). Today, the most frequently used anticoagulants for chronic intermittent haemodialysis (IHD) are unfractionated heparins (UFH) and low-molecular-weight heparins (LMWH) (3). There are well established methods for the application of these agents during dialysis and their use is generally simple and rather safe. However, chronic exposure to UFH and to lesser extend to LMWH is not unproblematic due to the potential risk of hyperlipidemia (4–9), osteoporosis (10, 11), alopecia (12), skin alterations (13, 14) and/or antibody-mediated heparin-induced thrombocytopenia (15). The use of UFH is characterised by an important intra- and interpatient variability of the anticoagulation efficacy and a lack of reliable pharmacodynamic and pharmacokinetic models. Systemic anticoagulation during the dialysis session with UFH may be associated with potentially life threatening haemorrhagic events. Less bleeding problems appear to be associated with LMWH due to their predominant effect on factor Xa as compared with factor IIa (5, 16–18) and possibly with their reduced inhibition of thrombin activatable fibrinolytic inhibitor (TAFI) (19). Therapeutic monitoring is usually not recommended during LMWH therapy. If required, measurement of anti-Xa is advocated (20). However, anti-Xa activity has been shown to correlate poorly with the anticoagulant efficacy during LMWH-therapy (21). Furthermore it has been shown that a decrease in renal elimination of LMWH in patients

Correspondence to:
Dominik E. Uehlinger
Universität Bern
Klinik und Poliklinik für Nephrologie und Hypertonie, Inselspital
Freiburgstrasse 15, 3010 Bern, Switzerland
Tel.: +41 31 632 31 44, Fax: +41 31 632 97 34
E-mail: uehlinger@mph.unibe.ch

Received July 6, 2007
Accepted after revision September 22, 2007

Prepublished online November 9, 2007
doi:10.1160/TH07–07–0444

with renal failure may result in a dangerous accumulation with the risk of bleeding episodes (22, 23).

Fondaparinux sodium (Arixtra®, GlaxoSmithKline, Brentford Middlesex, UK, former Sanofi-Synthélabo, Paris, France) is the first member of a new class of synthetic inhibitors of factor Xa. It is a pentasaccharide with a molecular structure comprising the active binding site of both UFH and LMWH to antithrombin (AT). It has neither an effect on factor IIa (thrombin) nor on platelets. In several large clinical studies fondaparinux sodium revealed an equivalent or superior efficacy compared to LMWH in terms of thromboprophylaxis after orthopaedic and surgical interventions as well as in acutely ill medical patients with a similar safety profile (24–26). Since fondaparinux sodium is probably deprived of collateral metabolic and immunologic effects such as hyperlipidemia, osteoporosis or antibody-mediated thrombocytopenia, its use as an anticoagulant for chronic haemodialysis appears therefore suitable (27). However, the exclusive renal elimination and the long half-life have so far precluded the use of fondaparinux in end-stage renal disease (ESRD) patients.

In the presented prospective open-label study, we compared fondaparinux sodium with standard UFH anticoagulation during chronic haemodialysis therapy in terms of efficacy and safety, with a main focus on the pharmacokinetic/phamacodynamic proprieties of fondaparinux.

Subjects and methods

Subjects

Twelve stable patients with ESRD were recruited for this study. All patients had been on regular haemodialysis therapy for at last six months prior to the study. They were dialyzed thrice weekly with a dialysis treatment time of 180 to 240 minutes (min) (mean ± standard deviation [SD] 204 ± 20 min). Haemodialysis was performed using hollow-fibre dialysers (F60S, HF80S, HdF100S; Fresenius Medical Care, Bad Homburg, Germany) and a single-pass dialysate delivery system (Miroclav; Dialysetechnik / Baxter, Ettlingen, Germany). All dialysers were prerinsed with 1,000 ml 0.9% saline, without the addition of UFH. Dialysis treatment parameters are given in Table 1. The age of the patients ranged from 25 to 84 years with a mean age of 57.7 ± 18.6 years, four patients were female (Table 2).

All patients had regular anticoagulation during the dialysis procedure with porcine UFH (Liquemin®, Roche, Basel, Switzerland), with stable dosing and no thrombotic or bleeding problems observed for at least one month prior to the investigation. All but two patients were additionally treated with 100 mg acetylsalicylic acid for primary or secondary prevention of cardiovascular diseases. None of the patients received oral anticoagulant therapy.

Exclusion criteria were: History of acute or chronic haemorrhage, thrombocytopenia, known intolerance to heparin and heparinoids, severe hepatic disease, proteinuria > 3g /day, pregnancy or lactation, and intellectual restriction to understand the study. The protocol was approved by the state ethics committee (Kantonale Ethikkommission Bern, Switzerland), and written informed consent was given by each patient prior to participating in this study.

Table 1: Haemodialysis treatment parameters.

Dialysis treatment time, min	204 ? 20
Filter HF60S : HF80S : HdF100S*	3 : 7 : 2
Blood flow rate, ml/min	388 ± 33
Dialysate flow rate, ml/min	500
Predialysis weight, kg	72.8 ± 11.9
Postdialysis weight, kg	71.2 ± 11.7
eKt/V+	1.23 ± 0.24

Values are mean ± SD. *polysulfone hollow fiber filters (Fresenius Medical Care, Bad Homburg, Germany). +equilibrated Kt/V[29].

Table 2: Patient characteristics.

	N = 12
Age, years	57.7 ± 18.6
Race, caucasian	12
Gender, male	8
Weight, kg	72.8 ± 11.9
Time on dialysis, years	3 (0.5–16)*

Values are mean ± SD. *Median (range).

Study design

Run-in phase I

During the run-in phase, all patients were treated with their regular dialysis and anticoagulation prescription. As usual, UFH was administered as a priming dose injected directly into the arterial line of the extra-corporeal circuit followed by a maintenance infusion that lasted until one hour before the end of dialysis.

Anticoagulation efficacy was assessed by a semiquantitative clotting score (SQCS). At the end of each dialysis procedure, filter and tubing were examined by the dialysis nurse after rinsing the circuit with 150 ml saline. Clotting scores were assigned as follows: "0" for a clean filter and no visible clots in the drip chambers; "1" for traces of coagulation in the filter and/or in the drip chambers; "3" for a fully clotted extracorporal system resulting in an interruption of the dialysis session and "2" for an intermediary state between "1" and "3". Adequate anticoagulation was defined by a SQCS of less or equal "1".

For the detection of an enhanced bleeding tendency, a standardized assessment of the arterial and venous puncture site compression times was performed. Initial standardized compression times for the arterial and venous puncture sites of each patient were derived by reducing the historically used empirical compression times by 10%. Both puncture sites were digitally compressed following removal of the cannulas for the exact initial standardized compression times. Puncture sites were then observed and if no bleeding occurred within 2 min after release of the compression, standardized compression times were deemed sufficient and were used for the following haemodialysis session. If bleeding was observed within 2 min after the release of the compression, the puncture site was recompressed,

and the standardized compression time for this puncture site was prolonged by 2 min after the next dialysis session. Bleedings observed later than 2 min after release of the compression were assessed but did not influence the future standardized compression times. Final standardized compression time, termed "supraminimal compression times", had to result in sufficient primary haemostasis on two consecutive haemodialysis sessions prior to qualify the patient for the next phase of the study.

Phase I

During phase I of the study, UFH was replaced once weekly after the long interdialytic interval by fondaparinux sodium (Arixtra®). The initial dose of fondaparinux sodium was calculated on a gravimetric basis of 0.05 mg per kg body weight (BW).

For the administration of fondaparinux sodium, one to three single-dose prefilled syringes (2.5 mg fondaparinux in 0.5 ml) were injected into an ampoule containing 20 ml of 0.9% saline. After mixing, the volume of the diluted solution corresponding to the prescribed dose was injected directly into the arterial line of the extra-corporeal circuit immediately before the beginning of the dialysis session. No maintenance dose of fondaparinux sodium was used.

The SQCS was obtained at mid-dialysis and at the end of each session. If the score did not exceed "1", anticoagulation was deemed sufficient and the same dose was used for the following dialysis session with fondaparinux sodium after a wash out period of one week (2 dialysis sessions with UFH). If, on the other hand, the semiquantitative clotting score exceeded "1", the amount of administred fondaparinux sodium was increased by 0.01 mg / kg BW after the next two washout dialysis sessions with UFH. This iterative weekly dose adaptation was performed until a sufficiently low clotting score or an occurrence of enhanced bleeding tendency was observed. Once again, such low anticoagulation scores had to be observed on two consecutive dialysis sessions prior to proceeding to the next phase of the study.

Anti-Xa-activity, D-dimers and prothrombin fragments F1+2 were measured in blood obtained before the filter at the start of dialysis, after 15 and 120 min and at the end of the dialysis session. In addition, measurements of these parameters were performed in blood obtained after the filter at 120 min.

At the end of each dialysis procedure, puncture sites were compressed to determine the supraminimal compression time (see above). If bleeding occurred within 2 min after the release of the compression, the reference value was increased by 2 min on the next dialysis session with fondaparinux sodium, otherwise it was kept constant.

During the two dialysis sessions with UFH anticoagulation following each session with fondaparinux sodium of phase I, patients were asked for adverse effects and for signs of an enhanced bleeding tendency, such as late bleeding at the puncture site during the interdialytic interval, haematomas, and suffusions. Furthermore, anti-Xa-activity was measured prefilter at the beginning of the first dialysis session with UFH anticoagulation following the dialysis session with fondaparinux sodium.

Run in phase 2

After a wash-out period of at least one week with standard UFH, standardized digital compression times were monitored following three consecutive dialysis sessions as described in phase I.

Phase 2

This phase of the study consisted of nine consecutive dialysis sessions (3 weeks) with fondaparinux sodium anticoagulation. It was originally planed to use the final fondaparinux sodium doses obtained during phase I, but due to some observed bleeding episodes at the puncture sites during phase one, the protocol was slightly modified and each patient received the same dose, i.e. 0.05 mg fondaparinux sodium / kg BW on the nine consecutive dialysis sessions. At the beginning of each dialysis session anti-Xa activity was measured in prefilter blood immediately before fondaparinux sodium was administered. Clotting scores and digital compression times were obtained as described above.

Analytical procedures

Coagulation parameters

Blood samples were collected from the prefilter haemodialysis tube into 0.106 mM tri-sodium citrate (9:1 vol/vol) in plastic syringes (Monovette®, Sarstedt, Nümbrecht, Germany) and centrifuged within 30 min. Platelet-poor plasma (PPP) containing less than 10,000 platelets per µl was prepared by double centrifugation at 1,500 g for 15 min at 20°C. The samples were aliquoted, snap-frozen and stored at –80°C until testing. Before testing, the plasma samples were thawed by immerging the tubes in a water bath at 37°C for 5 min and then briefly vortexed. Anti-factor Xa activity was measured by a commercial chromogenic method (Chromopep®, Chromogenix, Instrumentation Laboratory, Milano, Italy). D-dimer (Assechrom D-DI®, Diagnostica Stago) and prothrombin fragment 1+2 (Enzygnost F1+2 micro®, Dade Behring) were measured by quantitative sandwich enzyme immunoassay according to the manufacturers' protocols.

Statistical analyses

The software packages SAS 9.1 (SAS Institute Inc., Cary, NC, USA) and Systat 10 (SPSS Inc., Chicago, IL, USA) were used for statistical analyses. Values are given as mean ± SD if not indicated otherwise.

The pharmacokinetic model describing the disposition and elimination of fondaparinux over the whole observation period of three weeks (phase 2) was calculated with the computer program NONMEM V (nonlinear mixed effects modelling, NONMEM Project Group, University of California at San Francisco, CA, USA) on a Linux Cluster.

Results

All 12 patients enrolled completed the trail according to the study protocol. None of them had to be excluded for major side effects such as bleeding or for protocol violation. Patient characteristics and dialysis treatment parameters are given in Tables 1 and 2, respectively.

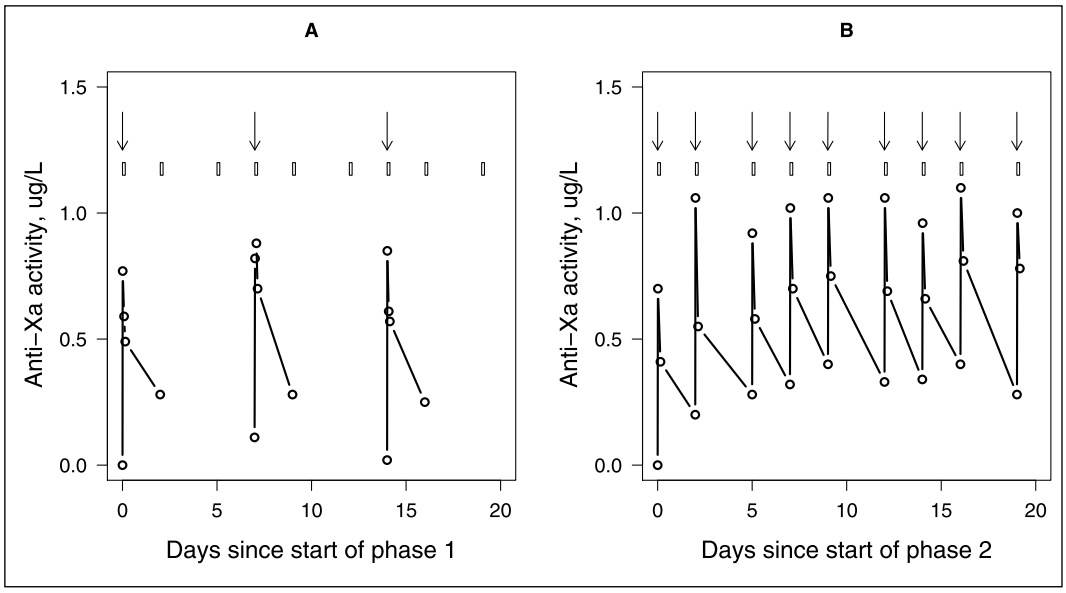

Figure 1: Plasma anti-Xa activity in µg/l, in an individual patient during phase 1 (A) and phase 2 (B). Intravenous bolus doses of fondaparinux sodium (arrows) were given immediately before dialysis procedures once weekly (phase 1) or thrice weekly (phase 2). Times on dialysis (210 min per session) are indicated by the rectangles below the arrows.

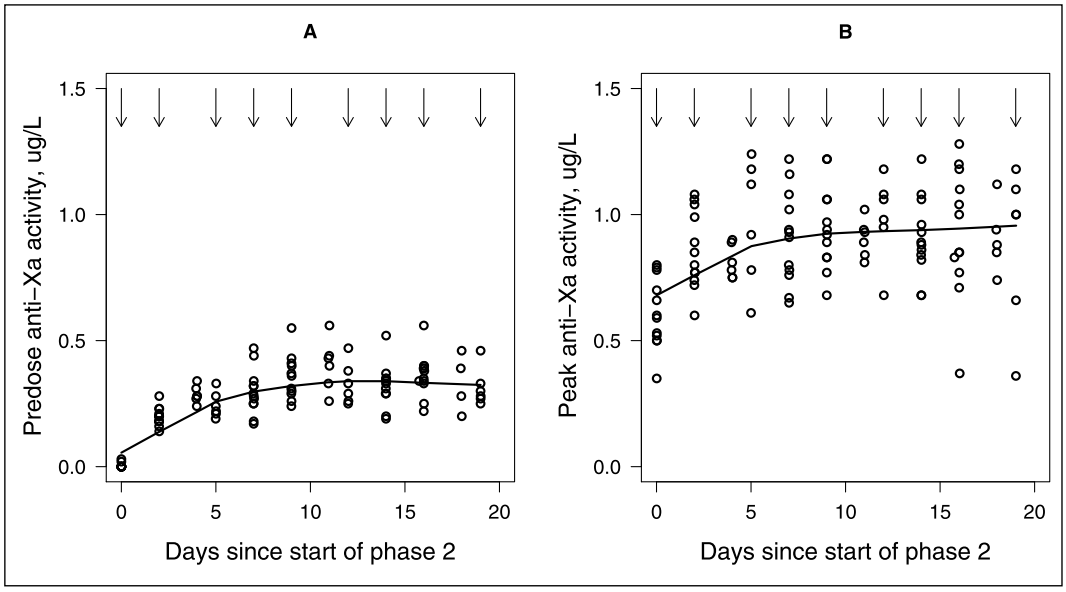

Figure 2: Plasma anti-Xa activity during phase 2 comprising nine consecutive dialysis sessions with fondaparinux sodium bolus injection immediately before the dialysis procedure.
A) Trough (pre-dose) anti-Xa activity. B) Peak anti-Xa activity . The lines represent locally weighted least squares smoothing (LOWESS).

Run-in phase

For each patient five standard dialysis sessions were monitored. To achieve sufficient anticoagulation, 4,825 ±1,703 U (N=60) of UFH, representing the sum of bolus and maintenance dose, were required. Mean semiquantitative clotting score (SQCS) was 0.65 ± 0.58 (N=60). In one patient, one dialysis treatment session had to be terminated prematurely due to clotting of the extracorporeal circuit (SQCS = 3). The supraminimal fistula compression time calculated according to the algorithm was 23.7 ± 7.4 min and served as a reference time in further part of the study.

Phase I

Anticoagulation with fondaparinux sodium at the starting dose of 0.05 mg / kg BW resulted in a sufficient anticoagulation with a SQCS of "1" in two patients. The remaining patients underwent more than two dialysis sessions with fondaparinux sodium with increased doses, mostly 0.06 mg / kg BW. In one patient, the fondaparinux sodium dose had to be increased to 0.08 mg / kg BW.

Regardless of the fact that all dialysis sessions with fondaparinux sodium anticoagulation could be completed, the latter appeared less efficient than standard UFH anticoagulation resulting in more clotted filters and marked fibrin deposition in the drip chambers. Mean SQCS of all dialysis sessions of phase I with the fondaparinux sodium anticoagulation was 1.6 ± 0.73 as compared with the 0.65 ± 0.58 during UFH anticoagulation ($p<0.0005$). Thus there was a significant difference in anticoagulation efficacy in favour of UFH. There was no significant improvement of anticoagulation efficacy by increasing the dose of

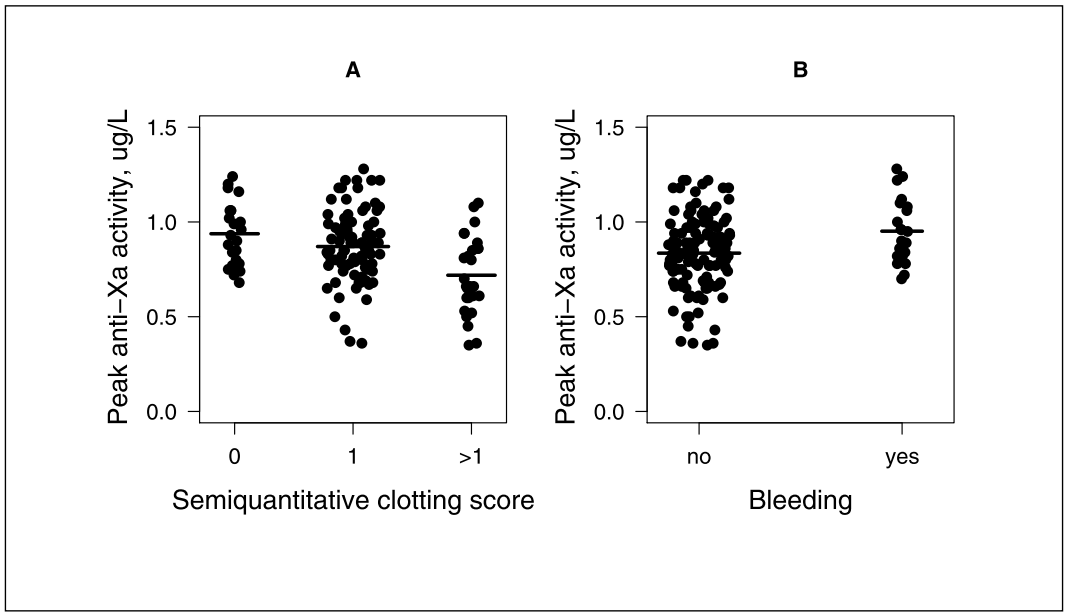

Figure 3: Clinical implications of anti-Xa activity. A) Relationship between semiquantitative clotting scores and peak anti-Xa activities. Clotting scores were assigned as follows: "0" for a clean filter and no visible clots in the drip chambers; "1" for traces of coagulation in the filter and/or in the drip chambers; "3" for a fully clotted extracorporal system resulting in an interruption of the dialysis session and "2" for an intermediary state between "1" and "3". B) Bleeding episodes observed later than 2 min after compression at the puncture sites. Bleeding episodes were observed at higher peak anti-Xa activities ($p < 0.02$). The lines represent mean values.

fondaparinux sodium from 0.05 mg/kg BW to 0.06 mg/kg BW: SQCS 1.7 ± 0.49 versus 1.5 ± 0.84. The bleeding tendency was clearly enhanced with a slight but significant extension of the supraminimal fistula compression times from 23.7 ± 7.4 min initial to 24.8 ± 7.5 min at the end ($p<0.05$). In addition, six of the 12 patients reported bleeding from the puncture sites during the interdialytic interval.

Prothrombin activation fragment F1+2 significantly increased during haemodialysis sessions from 1.9 ± 0.6 ng/l before fondaparinux sodium application to 2.1 ± 0.7, 2.7 ± 1.7 and 3.0 ± 1.6 at 15 min, 2 hours (h) and at the end of the dialysis procedure, respectively (all differences significant). A similar trend was observed for D-dimer, that tended to increased from 969 ± 853 ng/l to 997 ± 906, 1,048 ± 943 and 1,157 ± 972, respectively, during the dialysis procedures (T_0 vs. T_{END}: $p<0.007$).

No concentration differences of anti-Xa activity, prothrombin activation fragment F1+2 or D-dimer were observed when blood samples were drawn after the filter at 2 h as compared with the usual prefilter determinations at the same time point.

Phase 2

Administration of 0.05 mg fondaparinux sodium / kg BW at the start of nine consecutive dialysis sessions resulted in an increase of predialysis anti-Xa activity from 0.00 ± 0.01 to 0.32 ± 0.09 µg/l and of the peak anti-Xa activity after drug administration from 0.61 ± 0.14 to 0.89 ± 0.24 µg/l (Figs. 1, 2). SQCS decreased during these nine consecutive dialysis from 1.50 ± 0.52 to 1.00 ± 0.43 ($p<0.05$) and puncture site compression times increased from 23.9 ± 7.5 to 26.3 ± 9.2 min ($p<0.05$).

Patients treated with 100 mg/day acetylsalicylic acid tended to show prolonged fistula compression times (+ 8.2 min) and a more pronounced prolongation during treatment with fondaparinux as compared with the two patients without additional antiaggregant therapy. No effect on filter patency was observed by the additional antiaggregant therapy.

Figure 3 shows the weak relationships between measured anti-Xa activity and observed SQCS and bleeding episodes (both phases combined). While clotting tended to be lower at higher peak anti-Xa activities, the only complete clotting of the extracorporal system (clotting score "3") was observed at an anti-Xa activity of 0.94 µg/l. Bleeding episodes later than 2 min after compression were observed at higher peak anti-Xa activities ($p < 0.02$). No bleeding episodes were observed when the peak anti-Xa activity was below 0.7 µg/l. On the other hand, one patient with an observed maximum peak anti-Xa levels of 0.71 µg/l, did no longer show normal scarring of puncture sites (Fig. 4).

Pharmacokinetics of fondaparinux

A nonlinear mixed effects model was used to describe fondaparinux drug disposition (measured as anti-Xa activity) during the whole observation period of phase 2, i.e. three weeks with nine consecutive dialysis sessions.

Changes of plasma fondaparinux concentrations (dC/dt) (measured as anti-Xa activity) were modelled as

$$dC/dt = -(ClrR + I*ClrD)/V * C(t)$$

where:

Clr_R = *total clearance off dialysis*

Clr = additional clearance induced by dialysis

I = dialysis indicator variable: 1 during dialysis, 0 otherwise

This basic model resulted in a good, unbiased fit (Fig. 5). Predicted population parameters are given in Table 3. The model could neither be improved, when Clr_D was linearly related to the expected dialysis urea clearance values (K) derived from individual eKt/V calculations (minimum objective function –1,304.1 vs. –1,298.5) nor when the distribution volume V was linearly related to postdialysis BW (minimum objective function –1,293.2 vs. –1,298.5).

Discussion

In the present investigation, the effect of the novel pentasaccharide fondaparinux sodium was compared for the first time with UHF for anticoagulation during haemodialysis treatment. The SQCS revealed that anticoagulation during dialysis sessions was less pronounced with fondaparinux sodium as compared with standard UFH. This finding can either be explained by an insufficient dose of fondaparinux or by an intrinsic weaker effect of fondaparinux in preventing clotting of the dialyser and/or blood lines due to its pharmacodynamic or pharmacokinetic properties. The explanation of an insufficient dose is unlikely since successive increases of the dose of fondaparinux sodium did not significantly lower the semiquantitative clotting score in the first part of the study indicating the possibility of a ceiling of the dose-response curve. On the other hand, the achievement of high trough anti-Xa activity in the second part of the study due to the accumulation of fondaparinux was associated with slightly improved filter patency rates, demonstrating at least some additional effect at higher concentrations. However, increased doses resulted in unacceptable prolonged fistula compression times and interdialytic bleeding from fistula puncture sites consistent with enhanced systemic anticoagulation. Finally, the achieved anti-Xa activity trough levels were in or even above the upper range recognized for therapeutic systemic anticoagulation. The significant and steady increase of prothrombin fragment F1+2 and D-dimer during haemodialysis procedures underline the observation of insufficient anticoagulation achieved in the filter and/or tubes reflecting increased thrombin formation and consecutive fibrinolysis. Unfortunately, these coagulation parameters were not measured during standard haemodialysis procedures with UFH and the meaning of the observed increase under fondaparinux is therefore difficult to judge.

The explanation for the apparent inferiority of fondaparinux sodium compared to UFH in achieving sufficient anticoagulation of the extracorporeal circuit remains speculative. Since an inappropriate dosing of fondaparinux sodium does not seem to be responsible for the insufficient anticoagulation, pharmacodynamic differences between fondaparinux and UHF might be relevant. Fondaparinux sodium is characterised by a lack of factor IIa inhibition and platelet interaction. Thus, it is reasonable to infer that the sequential blockade at different sites of the coagulation system achieved by UHF, independently of platelet antiagregation with acetylsalicylic acid, might be an advantage in anticoagulation of the extracorporeal circuit. In addition, fondaparinux does not promote release of tissue factor pathway inhibitor (TFPI) from the vascular endothelium, an important mediator of the in-vivo antithrombotic properties of UFH and LMWH (28). Finally, a possible explanation might result from the biophysical properties of UFH. As a macromolecule, UFH is able to coat the extracorporeal circuit with a gel layer and may therefore prevent activation of the coagulation system by bioincompatible surfaces such as filters and tube lines.

During this study, the dose of fondaparinux sodium was increased in case of insufficient anticoagulation based on the clotting score. Due to the observed ceiling of the dose-response curve when anti-Xa activity was considered, it would be interesting to test lower doses of fondaparinux sodium with the expectation of a reduced risk of bleeding despite similar anticoagulant efficacy.

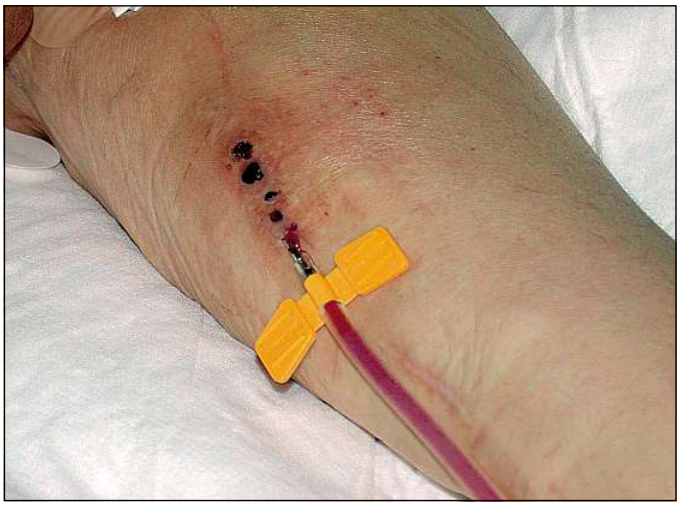

Figure 4: Native fistula from one of the study patients. The photograph shows the puncture site of the arterial (prefilter) canula – the puncture site of the venous (postfilter) canula is located more proximal and is not shown. Each of scabs resulted from a single dialysis session i.e. the oldest scab is about 10 days old.

Table 3: Population pharmacokinetic parameters estimated from changes in anti-Xa activity.

	Population mean value	Coefficient of variation
Clr_R[1], ml/min	1.12	14.3 %
Clr_D[2], ml/min	9.79	27.8 %
V, L	5.94	19.6 %
Random error		10.8 %

[1]total clearance if not on dialysis, [2]additional clearance induced by dialysis. Changes of plasma fondaparinux concentrations (dC/dt) (measured as anti-Xa activity) were modelled as: dC/dt = – (ClrR+I*ClrD)/V * C(t). Where: Clr_R=total clearance off dialysis, Clr=additional clearance induced by dialysis, I = dialysis indicator variable: 1 during dialysis, 0 otherwise.

The clearance of fondaparinux increases about 10-fold during haemodialysis sessions (Table 3). Nevertheless, the total clearance of fondaparinux remains low, resulting in an accumulation of the drug and resulting in high anti-Xa levels during dialysis sessions. These levels remain high until 48 h after the haemodialysis procedure, given the long half-life of about 60 h off dialysis. This pharmacokinetic "disadvantage" in patients with renal failure may represent a potential benefit for patients requiring long-term anticoagulation. The hypothetical advantage of a long-term anticoagulation based solely on intravenous drug administration during dialysis procedures must be weighted against possible side effects from the use of fondaparinux during dialysis. We have observed in some patients a slowed scaring and breaking of scabs with late bleeding from the puncture sites (Fig. 4). The safety of fondaparinux sodium with regard to wound healing has not yet been systematically investigated, although smaller trials comparing enoxaparin to fondaparinux so-

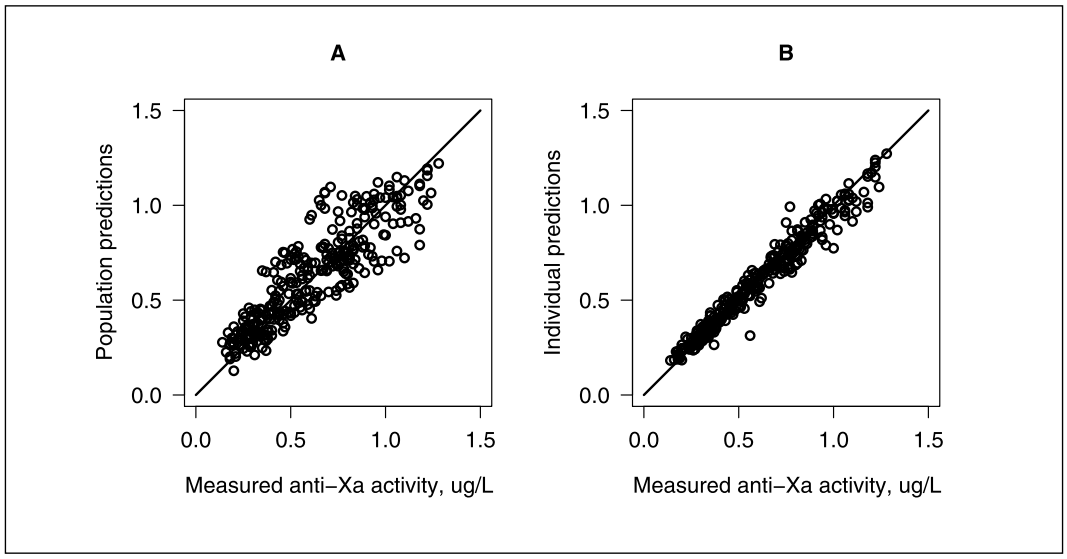

Figure 5: Predicted versus measured anti-Xa activities over the whole observation period of three weeks (i.e. 9 dialysis sessions).
A) Population predictions.
B) Individual predictions. The lines represent the identity lines.

dium did not find significant differences after major knee surgery (29).

In conclusion, fondaprinux sodium exhibits very predictable pharmacokinetics which allows to anticipate anti-Xa activity and to adapt the dosage accordingly. In the present study, anticoagulation achieved with fondaparinux sodium was clearly inferior as compared with UFH. Nevertheless, all but one dialysis session could be finished without the need for an exchange of the dialyzer and/or tubing. The slow elimination of fondaparinux sodium results in accumulation with risk of bleeding complications but the potential benefit of intradialytic anticoagulation. Thus, anticoagulation with fondaparinux administration during dialysis sessions is an interesting alternative for patients requiring long-term anticoagulation. In patients with documented heparin-induced thrombocytopenia, specifically in those cases where LMWH also cross-react, fondaparinux might be the anticoagulant of choice. In order to assess the risk-benefit ratio a large clinical trial should be performed.

Conflict of interest

The authors have received the study drug free of charge and a fee to cover the expense of additional laboratory work from Sanofi-Synthelabo®.

References

1. Ambuhl PM, Wuthrich RP, Korte W, et al. Plasma hypercoagulability in haemodialysis patients: impact of dialysis and anticoagulation. Nephrol Dial Transplant 1997; 12: 2355–2364.
2. Sagedal S, Hartmann A, Sundstrom K, et al. Anticoagulation intensity sufficient for haemodialysis does not prevent activation of coagulation and platelets. Nephrol Dial Transplant 2001; 16: 987–993.
3. Perry SL, O'Shea SI, Byrne S, et al. A multi-dose pharmacokinetic study of dalteparin in haemodialysis patients. Thromb Haemost 2006; 96: 750–755.
4. Schmitt Y, Schneider H. Low-molecular-weight heparin (LMWH): influence on blood lipids in patients on chronic haemodialysis. Nephrol Dial Transplant 1993; 8: 438–442.
5. Schrader J, Stibbe W, Armstrong VW, et al. Comparison of low molecular weight heparin to standard heparin in hemodialysis/hemofiltration. Kidney Int 1988; 33: 890–896.
6. Schrader J, Andersson LO, Armstrong VW, et al. Lipolytic effects of heparin and low molecular weight heparin and their importance in hemodialysis. Semin Thromb Hemost 1990; 16 (Suppl): 41–45.
7. Stefoni S, Cianciolo G, Donati G, et al. Standard heparin versus low-molecular-weight heparin. A medium-term comparison in hemodialysis. Nephron 2002; 92: 589–600.
8. Wiemer J, Scherberich JE. When lipids increase in dialysis: the role of heparin! Standard heparin increases, low-molecular-weight heparin lowers triglycerides. MMW Fortschr Med 1999; 141: 29–32.
9. Wiemer J, Winkler K, Baumstark M, et al. Influence of low molecular weight heparin compared to conventional heparin for anticoagulation during haemodialysis on low density lipoprotein subclasses. Nephrol Dial Transplant 2002; 17: 2231–2238.
10. Pettila V, Leinonen P, Markkola A, et al. Postpartum bone mineral density in women treated for thromboprophylaxis with unfractionated heparin or LMW heparin. Thromb Haemost 2002; 87: 182–186.
11. 11. Handschin AE, Trentz OA, Hoerstrup SP, Kock HJ, Wanner GA, Trentz O. Effect of low molecular weight heparin (dalteparin) and fondaparinux (Arixtra) on human osteoblasts in vitro. Br J Surg 2005; 92: 177–183.
12. Sarris E, Tsele E, Bagiatoudi G, et al. Diffuse alopecia in a hemodialysis patient caused by a low-molecular-weight heparin, tinzaparin. Am J Kidney Dis 2003; 41: E15.
13. Bredlich RO, Stracke S, Gall H, et al. Heparin-associated platelet aggregation syndrome with skin necrosis during hemodialysis. Dtsch Med Wochenschr 1997; 122: 328–332.
14. Ludwig RJ, Schindewolf M, Utikal J, et al. Management of cutaneous type IV hypersensitivity reactions induced by heparin. Thromb Haemost 2006; 96: 611–617.
15. Greinacher A, Farner B, Kroll H, et al. Clinical features of heparin-induced thrombocytopenia including risk factors for thrombosis. A retrospective analysis of 408 patients. Thromb Haemost 2005; 94: 132–135.
16. Gregorini G, Bellandi D, Martini G, et al. Heparin-induced thrombocytopenia syndrome and thrombosis in patients undergoing periodic haemodialysis. G Ital Nefrol 2002; 19: 672–692.
17. Lord H, Jean N, Dumont M, et al. Comparison between tinzaparin and standard heparin for chronic hemodialysis in a Canadian center. Am J Nephrol 2002; 22: 58–66.
18. Momi S, Nasimi M, Colucci M, et al. Low molecular weight heparins prevent thrombin-induced thrombo-embolism in mice despite low anti-thrombin activity. Evidence that the inhibition of feed-back activation of thrombin generation confers safety advantages over direct thrombin inhibition. Haematologica 2001; 86: 297–302.
19. Florian-Kujawski M, Hoppensteadt D, Maddineni J, et al. Differential regulation of thrombin activatable fibrinolytic inhibitor by low molecular weight heparins. Pharmacologic implications. Int Angiol 2004; 23: 346–354.
20. Linkins LA, Julian JA, Rischke J, et al. In vitro comparison of the effect of heparin, enoxaparin and fondaparinux on tests of coagulation. Thromb Res 2002; 107: 241–244.

21. Shinoda T, Arakura H, Katakura M, et al. Usefulness of thrombelastography for dosage monitoring of low molecular weight heparin and unfractionated heparin during hemodialysis. Artif Organs 1990; 14: 413–415.
22. Farooq V, Hegarty J, Chandrasekar T, et al. Serious adverse incidents with the usage of low molecular weight heparins in patients with chronic kidney disease. Am J Kidney Dis 2004; 43: 531–537.
23. Guillet B, Simon N, Sampol JJ, et al. Pharmacokinetics of the low molecular weight heparin enoxaparin during 48 h after bolus administration as an anticoagulant in haemodialysis. Nephrol Dial Transplant 2003; 18: 2348–2353.
24. Bauersachs RM. Fondaparinux: an update on new study results. Eur J Clin Invest 2005; 35 (Suppl 1): 27–32.
25. Turpie AG, Eriksson BI, Lassen MR, et al. Fondaparinux, the first selective factor Xa inhibitor. Curr Opin Hematol 2003; 10: 327–332.
26. Turpie AG. Fondaparinux: a Factor Xa inhibitor for antithrombotic therapy. Expert Opin Pharmacother 2004; 5: 1373–1384.
27. D'Angelo A, Valle PD, Fattorini A, et al. Disappearance of anti-PF4/heparin antibodies under prolonged fondaparinux administration in a patient with DVT associated with LMWH-induced thrombocytopenia. Thromb Haemost 2006; 95: 573–575.
28. Walenga JM, Jeske WP, Samama MM, et al. Fondaparinux: a synthetic heparin pentasaccharide as a new antithrombotic agent. Expert Opin Investig Drugs 2002; 11: 397–407.
29. Bonneux IM, Bellemans J, Fabry G. Evaluation of wound healing after total knee arthroplasty in a randomized prospective trial comparing fondaparinux with enoxaparin. Knee 2006; 13: 118–121.
30. Eknoyan G, Beck GJ, Cheung AK, et al. Effect of dialysis dose and membrane flux in maintenance hemodialysis. N Engl J Med 2002; 347: 2010–2019.