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Thoughts and Progress

Anticoagulation With Fondaparinux for Hemodiafiltration in Patients With Heparin-Induced Thrombocytopenia: Dose-Finding Study and Safety Evaluation

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Abstract: The optimal anticoagulation regimen for hemodialysis (HD) in patients with heparin-induced thrombocytopenia (HIT) has not been defined. Hemodiafiltration (HDF) adds a large convective component to HD, thereby changing the pharmacokinetics of most anticoagulants. Data on coagulation regimens for HDF are scant. We therefore aimed to study the feasibility, effectiveness, tolerability, and pharmacokinetics of fondaparinux anticoagulation in HDF. This was a prospective observational dose-finding study. Patients were started on fondaparinux at a dose of 0.05 mg/kg postdialysis body weight. Per protocol dose escalation was performed when significant clotting was observed and reduced when the anti-Xa activity postdialysis exceeded 0.4 IU/mL. Dose adjustments were made by steps of 0.01 mg/kg postdialysis weight. Anti-Xa activity was measured using a chromogenic method calibrated with low-molecular-weight heparin and validated against fondaparinux-calibrated anti-Xa activity. Four patients with HIT were followed for 160 sessions in total. At the end of the dose titration study, three patients ended at a maintenance dose of 0.03 mg/kg and one patient at 0.04 mg/kg of fondaparinux. Significant bleeding attributable to fondaparinux did not occur. The occurrence of clotting increased parallel to the reduction of fondaparinux dose, from 0/53 and 0/15 sessions at the higher doses (0.04 and 0.05 mg/kg) to 3/75 (4%) at 0.03 mg/kg and 1/17 (6%) at 0.02 mg/kg. Fondaparinux may be safely used and provides adequate anticoagulation for HDF in patients with HIT. We recommend to adjust dosage of fondaparinux to body weight and to initiate therapy at a dose of 0.03 mg/kg to prevent accumulation. Dose titration can be achieved by targeting postdialysis anti-Xa activity. **Key Words:** Heparin-induced thrombocytopenia—Hemodiafiltration—Anticoagulation—Fondaparinux—Anti-Xa activity.

Anticoagulation is one of the supporting pillars of chronic hemodialysis (HD) (1). The optimal anticoagulant regimen results in full anticoagulation of the extracorporeal circuit with minimal systemic effects and comes at an affordable cost. Unfractionated heparin (UFH) has been the standard of care for many years, but in several countries it has gradually been replaced by low-molecular-weight heparins (LMWHs) (1). While this provides adequate anticoagulation in most patients, immunization to heparin may develop, potentially leading to heparin-induced thrombocytopenia (HIT) (2). Reported prevalences of clinically relevant HIT in HD patients differ substantially and vary from 0.3 to nearly 4% (3,4). Alternative anticoagulation protocols are a necessity for delivering dialysis to these patients. Whereas evidence-based guidelines help in choosing the optimal treatment of acute HIT episodes (5), evidence guiding the choice of the optimal anticoagulation in HD patients is less clear and center practices vary widely.

Fondaparinux, a synthetic (i.e., not derived from heparin) pentasaccharide with a molecular weight of 1728D, is a specific anti-Xa inhibitor. Pharmacokinetic studies show almost complete renal excretion as an unchanged compound with a terminal half-life of about 17 to 20 h (6). Several case reports and case series reported the use of fondaparinux in HD patients with HIT (7–10). Kalicki et al. demonstrated accumulation of fondaparinux despite increased clearances of fondaparinux during HD (9). Use of high-flux dialyzers increased clearance of fondaparinux and was associated with an increased risk of clotting of the extracorporeal circuit and dialyzer (11). Hemodiafiltration (HDF) adds a large convective component to conventional HD, providing improved removal of larger (usually referred to as "middle") molecules (12). Data on anticoagulation during HDF in patients with HIT are scarce. Data on long-term safety and feasibility of fondaparinux in

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HDF are nonexistent. We therefore aimed to study the feasibility, tolerability, and pharmacokinetics of fondaparinux anticoagulation in HDF in a pilot study.

SUBJECTS AND METHODS

This was a single-center prospective observational dose-finding study. Study duration was 3 months, i.e., 40 consecutive dialysis sessions. Patients at the HD facility of the University Hospitals Leuven with HIT type II undergoing regional citrate anticoagulation for at least 3 months were eligible. Patients with an increased bleeding risk due to recent trauma or surgery, a history of bleeding, or anticoagulant therapy were not eligible, as were patients with short (<6 months) life expectancy and pregnancy. Informed consent was obtained from all study participants. The study was approved by the ethics committee of the hospital and was conducted in accordance with good clinical practice guidelines and ethical principles of the Helsinki Declaration.

Before inclusion patients received 4 h HD sessions three times per week. During the study period, patients were switched to post-dilution HDF. Dialysis blood flow rates had to be at least 250 mL/min. Dialysate flow rates were fixed at 500 mL/min. The Polyflux 170H dialyzer (Gambro Lundia AB, Lund, Sweden) was used for all treatments. Dialyzer membranes were not reused. At the start of each session, a single dose of fondaparinux (Arixtra, GlaxoSmithKline, Brentford, Middlesex, UK) was administered. One or two 2.5-mg fondaparinux in 0.5-mL prefilled syringes were injected into a single volume containing 20 mL of 0.9% saline. After mixing, volumes of this solution corresponding to the right dosage were injected into the efferent line of the dialyzer. The initial dosage of fondaparinux was 0.05 mg/kg postdialysis body weight. Per protocol dose escalation was performed when during three consecutive dialysis sessions significant clotting was observed, defined as preterm end of the dialysis session or failure to return extracorporeal blood volume to the patients. Per protocol dose reduction was performed if the anti Xa-activity at the end of dialysis exceeded that of 0.4 IU/mL LMWH. All dose adjustments were made by steps of 0.01 mg/kg postdialysis body weight. Clotting scores of the bubble trap and dialyzer were recorded after rinsing the line with 150 mL 0.9% saline. The occurrence of incipient clotting was judged by an experienced nurse using both objective (change in venous and trans-membrane pressures) and subjective (visual inspection of dialyzer and bubble trap) criteria. Visual inspection was scored according to a semiquantitative clotting score as used previously (Table 1) (13).

TABLE 1. *Semiquantitative clotting score*

Score	Dialyzer	Bubble trap
1	No signs of clotting	No signs of clotting
2	<50% area	Ring
3	>50% area	Clots in the bubble trap
4	Complete clotting	Complete clotting

The semiquantitative score clotting score was calculated from the sum of dialyzer and bubble trap degree of clotting.

Blood samples were collected into 0.106 mM trisodium citrate tubes (9:1 vol/vol) and centrifuged within 30 min. Platelet-poor plasma containing less than 10 000 platelets per μL was prepared by double centrifugation at 1500 × *g* for 15 min at 20°C. Samples were aliquoted, snap-frozen, and stored at –80°C until testing. For batch analysis, plasma samples were thawed using a water bath at 37°C for 5 min. Anti-factor Xa activity was measured weekly using a commercial chromogenic method (Chromopep, Chromogenix, Instrumentation Laboratory, Milan, Italy) calibrated with LMWH (Clexane, Sanofi Aventis, Diegem, Belgium). Limit of detection (LOD) was 0.1 IU/mL. Based on previous studies, we assumed that the anti-Xa activity (IU)/mL LMWH could be used as a proxy for fondaparinux activity (14). Therefore, per protocol dose adjustments were made using this assay. After completion of the study, fondaparinux concentrations were measured using a commercial chromogenic method (Chromopep) calibrated with fondaparinux. The LOD of the assay was 0.1 μg/mL.

Continuous variables are expressed as mean (standard deviation) for normally distributed variables or median (interquartile range) otherwise. A two-sided $P < 0.05$ was considered significant. For method comparison using Deming regression and Bland Altman plotting, we used Analyse-It (version 2.24, Analyse-It software LTD, Leeds, UK). For statistics, the SAS (version 9.1, the SAS institute, Cary, NC, USA) software package was used.

RESULTS

We screened 141 chronic dialysis patients for eligibility. Five patients (3.5%) fulfilled the inclusion criteria. One patient was excluded because of short life expectancy. All four eligible patients provided informed consent. Patient characteristics are given in Table 2. Patient age was between 63 and 84 years, gender distribution was even (two males, two

TABLE 2. *Patient demographics*

	Patient 1	Patient 2	Patient 3	Patient 4
Age (years)	63	80	71	84
Time on RRT (months)	76	95	54	10
Access	AV	AV	AV	AV
spKt/V	1.42	1.26	1.75	1.34
Gender	Male	Male	Female	Female
Weight (kg)	65.5	89	58.3	64.3
Antiplatelet agents (dose/day)	ASA (40 mg)	ASA/Dipyridamole (40/400 mg)	None	None
ESA dose (IU/kg/w)	126	125	400	249
Hemoglobin (g/dL)	10.6	10.7	10.9	10.1
Thrombocytes ($\times 10^3/mm^3$)	197	202	138	97
Dialyzer	PF 170H	PF 170H	PF 170H	PF 170H

RRT, renal replacement therapy; spKt/V, single pool Kt/V; ESA, erythropoietin stimulating agent; AV, arteriovenous fistula; ASA, acetylsalicylic acid.

females). Two patients were on chronic antiplatelet therapy because of primary ($n = 1$) or secondary ($n = 1$) prevention. None of the patients had residual renal function. Vascular access was by arteriovenous fistula in all patients.

All patients were started on fondaparinux at a dose of 0.05 mg/kg. On this dose, neither clotting nor bleeding episodes were observed (Table 3). Per protocol dose reduction was necessary after on average three sessions (range 2–6 sessions, total 15 sessions), based on anti-Xa activity (median 0.46, range 0.33–0.63 IU/mL). All patients were continued on fondaparinux at a dose of 0.04 mg/kg for a total of 47 sessions. At this dose, no bleeding episodes and only two minor clotting episodes occurred. Eventually, further per protocol dose reduction was required in all patients, with a wide dispersion (2, 3, 15, and 27 sessions, respectively) between numbers of delivered dialysis treatments prior to reaching the threshold for dose reduction. All patients subsequently continued on fondaparinux at a dose of 0.03 mg/kg for a total of 74 sessions. Two patients completed the study period without further adjustments. One patient had a dose escalation due to occlusive clotting of the dialyzer and ended the study period on fondaparinux at a dose of 0.04 mg/kg. One patient had a further dose reduction to 0.02 mg/kg during 16 sessions, but ended the study period at a dose of 0.03 mg/kg after per protocol dose escalation. At the end of the dose titration study, three patients ended with fondaparinux at a dose of 0.03 mg/kg and one patient at a dose of 0.04 mg/kg. When dose per postdialysis weight was calculated toward total absolute dose, at the end of the study period, patients received fondaparinux doses ranging from 1.75 to 2.5 mg. Significant bleeding events attributable to fondaparinux did not occur (Table 3). One patient experienced a sudden fall of hemoglobin. One dialysis session was delivered on regional citrate anticoagulation awaiting exclusion of occult bleeding. Eventually, the patient was diagnosed with pneumonia and the reduced hemoglobin levels were deemed secondary to serious infection. The patient continued the study protocol uneventfully. Severe clotting of the extracorporeal circuit (Table 3) was infrequent (4/160 sessions, 2.5%). The occurrence of clotting increased parallel to the reduction of fondaparinux dose, from 0/53 and 0/15 sessions at the higher doses (0.04 and 0.05 mg/kg) to 3/75 (4%) at 0.03 mg/kg and 1/17 (6%) at 0.02 mg/kg. When looking at all clotting events, using a semi-quantitative clotting score (Tables 1 and 3), we observed no significant difference between doses of fondaparinux (analysis of variance [ANOVA] $P = 0.08$). Anti-Xa activity postdialysis increased

TABLE 3. *Fondaparinux dose and safety end points*

Dose (mg/kg)	Sessions (*n*)	Anti-Xa activity Predialysis IU/mL Mean (SD)	Anti-Xa activity Postdialysis IU/mL Mean (SD)	Bleeding (*n* [%])	Clotting (*n* [%])	Clotting score Mean (SD)
0.02	17	0.12 (0.03)	0.17 (0.02)	0 (0)	1 (6)	4.56 (1.19)
0.03	75*	0.17 (0.03)	0.30 (0.04)	0 (0)	3 (4)	3.89 (1.56)
0.04	53	0.19 (0.04)	0.36 (0.05)	0 (0)	0 (0)	3.34 (1.32)
0.05	15	0.22 (0.06)	0.46 (0.09)	0 (0)	0 (0)	3.67 (1.22)

* Anticoagulation was by citrate instead of fondaparinux in one dialysis session, awaiting exclusion of occult bleeding.

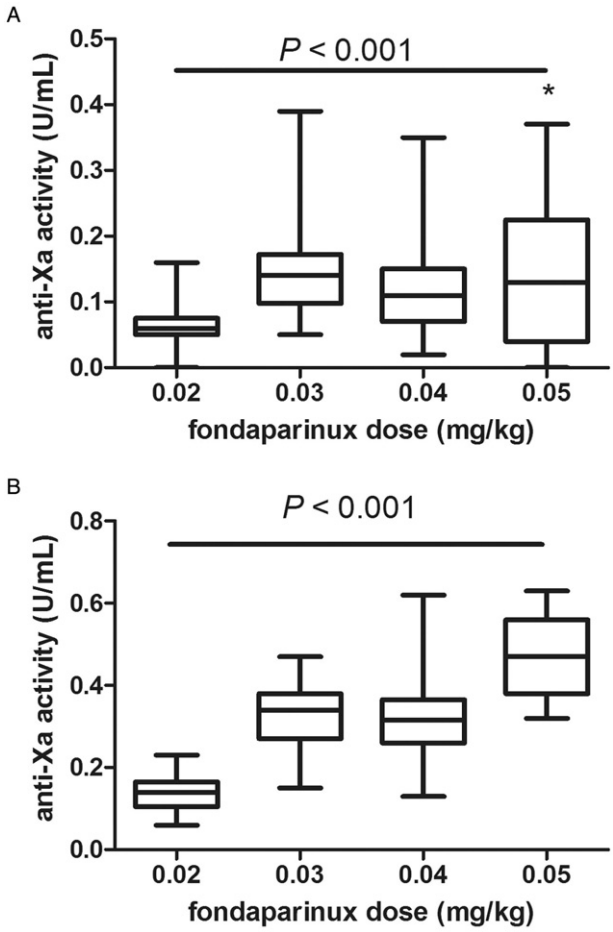

FIG. 1. Anti-Xa activity (A) predialysis and (B) postdialysis as a function of fondaparinux dose. Both pre- and postdialysis anti-Xa activity increased significantly with increasing dose of fondaparinux ($P < 0.001$ for both). *Post hoc analysis of predialysis anti-Xa activity shows a significant increase for fondaparinux at a dose of 0.05 mg/kg only (Tukey's test $P < 0.05$).

dose-dependently (ANOVA $P < 0.001$), as did anti-Xa activity predialysis (ANOVA $P < 0.001$) (Fig. 1). Analysis of the effect of the different doses on predialysis anti-Xa activity demonstrated a significant difference for fondaparinux at a dose of 0.05 mg/kg only. There were no episodes of thrombocytopenia or allergic events. No significant changes of epoetin alpha were needed. One patient received transfusion because of sepsis-mediated toxic anemia.

After completion of the study, we cross-validated the used anti-Xa assay calibrated with LMWH against fondaparinux concentrations quantified by a fondaparinux-calibrated anti-Xa assay (Fig. 2). In Deming regression analysis of pooled pre- and postdialysis samples, neither constant ($P = 0.4$) nor proportional ($P = 0.9$) bias could be observed (Deming fit $y = 1.02 \cdot x$—0.03).

DISCUSSION

HIT is a relatively rare but clinically relevant entity in dialysis patients. Choice of the optimal anticoagulation regimen is not defined and practice patterns differ widely. This is the first study investigating fondaparinux as anticoagulant in HDF. We demonstrate that fondaparinux is well tolerated and effective as anticoagulant for patients on HDF with known HIT.

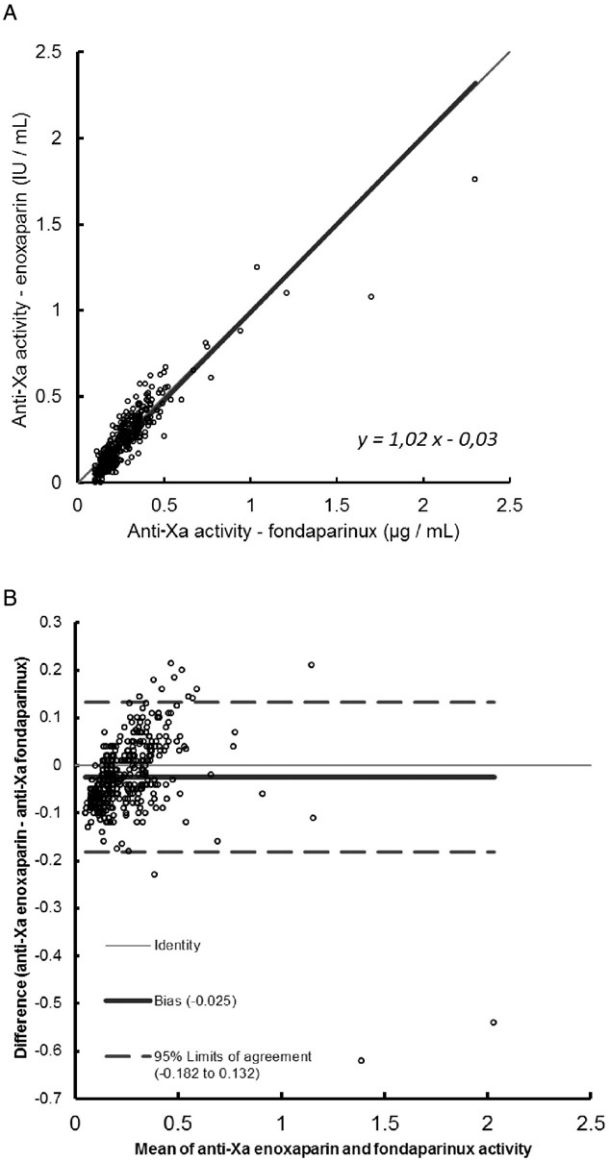

FIG. 2. Deming regression and Bland Altman analysis of anti-Xa enoxaparin activity versus fondaparinux activity. Deming regression demonstrates neither constant nor proportional bias. Bland Altman analysis overall shows good agreement with minimal bias (0.025 IU/mL). Two outliers with high anti-Xa activity suggest that at high concentrations, determination of anti-Xa activity underestimates blood concentrations of fondaparinux.

The optimal anticoagulation regimen requires a pharmacokinetic profile with adequate peak levels during dialysis and low trough levels during the interdialytic interval. Early observations suggested that the pharmacokinetic profile of fondaparinux is unfavorable, leading to accumulation in the interdialytic interval (9). The pharmacokinetic profile is influenced by dialyzer characteristics (low vs. high flux) (11). We speculated that HDF, by virtue of its increased convective transport, would increase clearance of fondaparinux. Distribution of fondaparinux is limited to the blood volume (6). Presuming that plasma volume associates with dry body weight, we therefore adjusted dosage of fondaparinux to postdialysis body weight. The starting dose of fondaparinux was selected from a previous study in which a bolus injection of 0.05 mg/kg fondaparinux in the afferent line prevented clotting formation but led to accumulation in HD (9). To minimize accumulation, dose reduction of fondaparinux was required when anti-Xa activity exceeded 0.4 IU/mL. This is strict considering that anticoagulation using UFH and LMWH results in postdialysis anti-Xa activity of approximately 0.3–0.4 IU/mL and 0.4–0.6 anti Xa IU/mL, respectively (1,15). Due to monitoring and dose titration, we were able to prevent accumulation (Table 3). During the 3-month study period totaling 160 dialysis sessions, we did not observe any significant bleeding episodes. From these observations, we suggest that fondaparinux can be used in patients with documented HIT receiving HDF. Rather than starting at a dose of 0.05 mg/kg, one may consider starting at a lower dose, e.g., 0.03 mg/kg. In case of clotting of the extracorporeal circuit, fondaparinux may then be titrated guided by trough levels of anti-Xa activity.

A limitation of this study is the small number of participants, as only patients with documented HIT were considered eligible to be included. A second limitation is that we included only stable maintenance dialysis patients. Fondaparinux exerts its anticoagulant effect by binding to the key heparin-binding site on antithrombin (1). Concentrations of antithrombin may be reduced in patients with liver failure or critical illness. We do not have data to support anticoagulation using fondaparinux in these patient populations. This study was designed to evaluate fondaparinux in patients with documented HIT. The favorable risk-benefit ratio warrants further evaluation in different patient populations as UFH and LMWH have been linked to osteoporosis and hyperlipidemia (16). So far, pleiotropic effects of fondaparinux have not been documented. Further studies are required to evaluate the full potential of fondaparinux in HD patients.

A point of interest is that we performed post hoc method comparison between conventional quantification of anti-Xa activity using LMWH as calibrator versus dedicated quantification of anti-Xa activity calibrated against fondaparinux. We observed good agreement between both assays in HD patients, confirming a previous study in healthy individuals (14). This is of clinical utility, as this allows to monitor fondaparinux therapy using conventional anti-Xa monitoring which is readily available in most clinical laboratories, thus obviating the need for specific calibration for fondaparinux.

CONCLUSION

This dose-finding study demonstrates that fondaparinux may be used as anticoagulant for hemodiafiltration in patients with heparin-induced thrombocytopenia. In contrast to previous reports, fondaparinux provides adequate anticoagulation without accumulation. We recommend to adjust dosage of fondaparinux to body weight and to initiate therapy at a dose of 0.03 mg/kg to prevent accumulation. Dose titration can be achieved by targeting postdialysis anti-Xa activity.

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