Fondaparinux as an alternative to vitamin K antagonists in haemodialysis patients

Marijn M. Speeckaert¹, Katrien M.J. Devreese², Raymond C. Vanholder¹ and Annemieke Dhondt¹

¹Department of Nephrology, Ghent University Hospital, Gent, Belgium and
²Department of Clinical Chemistry, Microbiology and Immunology, Ghent University Hospital, Gent, Belgium

Correspondence and offprint requests to: Marijn Speeckaert; E-mail: marijn.speeckaert@ugent.be

Keywords: anticoagulation, factor Xa inhibitor, haemodialysis

ABSTRACT

Background. Accelerated vascular calcification and increased risk of calciphylaxis can be a reason to restrict the use of vitamin K antagonists in dialysis patients. We describe the use of fondaparinux, a prototype indirect factor Xa inhibitor, as an alternative anticoagulant to coumarin derivatives in dialysis patients.

Methods. In this case series, we included six chronic haemodialysis patients treated with vitamin K antagonists. Low-molecular-weight heparin given as anticoagulant during dialysis was replaced by fondaparinux. Anti-Xa activity was regularly measured pre- and postdialysis to adapt the dose of fondaparinux. Adequate continuous anticoagulation and circuit patency were registered by evaluating clotting in the bubble trap and dialyser membrane at the end of dialysis.

Results. Anticoagulation with fondaparinux at a starting dose of 2.5 mg resulted in an effective anticoagulation in the majority of dialysis sessions. Although median predialysis anti-Xa levels were significantly lower [0.36 IU/mL (0.30–0.42 IU/mL) (P < 0.0001)] than postdialysis levels [0.75 IU/mL (0.65–0.80 IU/mL)], predialysis anti-Xa levels were sufficient to limit the risk of thromboembolism. After an initial period of gradually increasing anti-Xa levels due to accumulation of fondaparinux, stable levels were achieved. Haemodialysis without clotting problems was possible in 96% of the sessions (clotting score ≤1), whereas two episodes (2/459 dialysis sessions) of major clotting were observed, defined as clotting of the extracorporeal circuit necessitating premature termination of the procedure.

Conclusions. We demonstrated that fondaparinux is a valuable anticoagulant for patients dialysed with low-flux membranes in need of continuous anticoagulation.

INTRODUCTION

In the general population, current guidelines recommend the long-term use of oral anticoagulants for multiple conditions. Several recent publications have focused on the association between the use of vitamin K antagonists and the development of vascular calcification and atherosclerosis [1–8]. The inhibition of DT diaphorase [NAD(P)H dehydrogenase (quinone): EC.1.6.99.2] and vitamin K epoxide reductase by coumarins results in an undercarboxylation of vitamin K-dependent proteins such as matrix Gla protein (MGP), growth arrest-specific protein 6 and protein S, which play an important pathophysiological role in vascular biology and atherogenesis [9]. The subsequent medial calcification is a predictor for increased cardiovascular mortality and morbidity, which can be explained by its relationship with aortic stiffening, hypertension and myocardial infarction [10–12].

In patients with advanced chronic kidney disease (CKD) or end-stage renal disease (ESRD), data supporting the use of long-term oral anticoagulation are weak or absent [9]. CKD patients are particularly susceptible to vascular calcification and calciphylaxis (calcific uraemic arteriolopathy) due to an abnormal calcium/phosphate metabolism, a low vitamin K and vitamin D status and an exposure to uraemic retention products [10–14]. Vitamin K deficiency in haemodialysis patients may lead to an increased risk of over-anticoagulation and an impaired MGP carboxylation, contributing to an aggravated vascular calcification [9, 15–17]. There is a lack of intervention trials in haemodialysis patients addressing the potential therapeutic effect of vitamin K supplementation and the progression of vascular calcification.
At present, more selective anticoagulants such as direct thrombin or (in)direct factor Xa inhibitors are available as alternatives for vitamin K antagonists. Fondaparinux sodium \((C_{13}H_{43}N_{3}Na_{10}O_{49}S_{8}\text{ or SR90107A/Org31540})\) functions as a prototype of selective indirect factor Xa inhibitors [18]. Being composed of the antithrombin binding region of heparin, this synthetic pentasaccharide inhibits fibrin formation. This enhances the inactivation of factor Xa (by a factor of ±300) without interaction with factor II or platelets. Factor Xa is situated at the convergence of the intrinsic and extrinsic pathways of the coagulation cascade and is a key target for prophylactic anticoagulation [19, 20]. Several phase II and III trials have investigated the potential usefulness of fondaparinux in the general population: prevention/treatment of venous thromboembolism, heparin-induced thrombocytopenia (HIT), supraventricular tachycardia and acute coronary syndrome [21, 22].

As there is increasing evidence for the association between vitamin K deficiency and vascular calcification, therapeutic use of coumarin derivatives in haemodialysis patients may be questioned. We report here our experience with fondaparinux as an anticoagulant in haemodialysis patients previously treated with vitamin K antagonists.

**SUBJECTS AND METHODS**

Fondaparinux sodium (Arixtra®, GlaxoSmithKline, Middlesex, UK) was initially introduced in our dialysis unit for the treatment of a patient suffering from HIT. Subsequently, five patients receiving oral vitamin K antagonists (Mararevan®) for atrial fibrillation were switched to fondaparinux. Two patients had an arteriovenous fistula as vascular access. During the interdialytic interval, the catheters used in four patients were locked with citrate 30%. Low-flux membranes (Polysulfone FX8, Fresenius Medical Care, Bad Homburg, Germany) were used to limit the dialytic removal of fondaparinux in order to maintain anticoagulation during dialysis as well as during the interdialytic interval. The dialyser circuit was primed without heparin. Vitamin K antagonists were first stopped and replaced by daily low-molecular-weight heparin [LMWH: enoxaparin (dose: 40–80 mg/daily) or tinzaparin (dose: 3500–4500 units/daily)]. Subsequently, the LMWH given as anticoagulant during dialysis was replaced by a single bolus of 2.5 mg (being ±0.03 mg/kg) fondaparinux, injected in the inlet bloodline (arterial bloodline) of the extracorporeal circuit after the start of the session. Anticoagulation on non-dialysis days was withheld. After switch from LMWH to fondaparinux, anti-Xa activity was regularly measured pre- and postdialysis by a commercially available colorimetric assay (Biophen Heparin, HYPHEN BioMed, Neuville-sur-Oise, France). If the predialysis anti-Xa was too low (target: above 0.3 IU/mL), the dose was increased with 1.25 mg. If the postdialysis anti-Xa level was too high/too low (target: 0.6–1.0 IU/mL), the dose was adapted accordingly. Once stable anti-Xa activity was obtained, levels were checked monthly. Other coagulation parameters were not routinely determined as fondaparinux has no clinically relevant effect on fibrinogen, antithrombin or thrombin time [23]. Clotting rate in the bubble trap and dialyser membrane at the end of dialysis was staged routinely by visual inspection using a semiquantitative clotting score. The definition of clotting scores was as follows: 0 = clean filter and no visible clots in drip chambers, 1 = some traces of coagulation in filter and/or in drip chambers, 2 = a lot of traces of coagulation in filter and/or in drip chambers or presence of a clot, 3 = fully clotted extracorporeal system, necessitating premature termination of the procedure. A score of ≤1 was defined as a session with adequate anticoagulation and the dose of fondaparinux was maintained. If the semiquantitative clotting score exceeded 1, the dose was increased with 1.25 mg, with the limiting condition of a too high anti-Xa level. Bleeding events were defined as (i) a fall in haemoglobin by >3 g/dL, (ii) overt bleeding or (iii) an increase in compression time of the arteriovenous fistula by >50%. Statistical analyses were performed using MedCalc (MedCalc, Mariakerke, Belgium). Data are expressed as median and interquartile range (IQR) or as mean and the corresponding 95% confidence intervals. Differences between two groups were assessed by Mann–Whitney U-test. A P-value of <0.05 was considered to be statistically significant.

**RESULTS**

We report here our experience of the first 6 months of heparin-free haemodialysis (Table 1). Fondaparinux sodium was administered in six chronic haemodialysis patients (four males, two females, age: 65–85 years), who were receiving a 4-h conventional haemodialysis session (blood flow rate: 300–350 mL/min and dialysate flow rate with an autowater factor of 1.5) three times weekly. Four patients were anuric and two patients had a residual renal function (calculated as mean of urea and creatinine clearance) of 3.11 and 7.30 mL/min, respectively. The median postdialysis body weight at the first session with fondaparinux was 73.8 kg (IQR: 68.9–76.0 kg). Kt/Vurea values were 1.49 (IQR: 1.32–1.71). Anticoagulation with fondaparinux at a starting dose of 2.5 mg resulted in a sufficient anticoagulation in the majority of dialysis sessions. Although median predialysis anti-Xa levels were significantly lower [0.36 IU/mL (IQR: 0.30–0.42 IU/mL) (P < 0.0001)] than postdialysis [0.75 IU/mL (IQR: 0.65–0.80 IU/mL)], predialysis anti-Xa levels were sufficiently high to obtain a continuous anticoagulation without the risk of thromboembolism. Comparing the predialytic anti-Xa levels after a 2-day or a 3-day interdialytic interval, we found similar anti-Xa levels [predialysis after a 2-day interval: 0.37 IU/mL (IQR: 0.32–0.43 IU/mL) versus predialysis after a 3-day interval: 0.36 IU/mL (IQR: 0.30–0.41 IU/mL)] (P = 0.48). The elimination of fondaparinux is slowed down in patients with an impaired kidney function, a characteristic that is useful to bridge the interdialytic interval. Therefore, also the influence of the residual renal function on the predialysis anti-Xa levels was studied. Although the difference was not significant (P = 0.26), a trend was observed to relatively higher predialysis anti-Xa levels in anuric patients [0.37 IU/mL (IQR: 0.35–0.42 IU/mL)] in comparison with non-anuric patients [0.30 IU/mL (IQR: 0.28–0.44 IU/mL)]. Figure 1 illustrates the course of the mean
The dots within the brackets represent the mean of all anti-Xa levels measured during the following intervals: Week 0–2, Week 2–4, Week 4–10, Week 10–18 and Week 18–24, whereas the perpendicular lines within the brackets refer to the corresponding 95% confidence intervals during the first 6 months after the introduction of fondaparinux. After an initial period of gradually increasing anti-Xa levels due to accumulation of fondaparinux, stable levels were achieved. Haemodialysis without

**Table 1. Overview of patient and dialysis characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Present study</th>
<th>Kalicki et al. [28]</th>
<th>Sombolos et al. [29]</th>
<th>Ho et al. [30]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>6</td>
<td>12</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Age (y)</td>
<td>80 (70–83)</td>
<td>58 ± 19</td>
<td>62.6 ± 14.8</td>
<td>62.1 ± 16.1</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>4M/2F</td>
<td>8M/4F</td>
<td>4M/4F</td>
<td>6M/2F</td>
</tr>
<tr>
<td>Body weight (kg)a</td>
<td>73.8 (68.9–76.0)</td>
<td>71.2 ± 11.7</td>
<td>73.9 ± 19.2</td>
<td>71.5 ± 7.0</td>
</tr>
<tr>
<td>HD session (min)</td>
<td>240</td>
<td>204 ± 20</td>
<td>240</td>
<td>240</td>
</tr>
<tr>
<td>Dialysate type</td>
<td>Fx8 (low-flux)</td>
<td>3 × HF60S, 7 × HF80S, 2 × Hdf100S (high-flux)</td>
<td>FDX-18GW (high-flux)</td>
<td>ULF 18 (low-flux)</td>
</tr>
<tr>
<td>Blood flow rate (mL/min)</td>
<td>350 (300–350)</td>
<td>388 ± 33</td>
<td>300</td>
<td>300</td>
</tr>
<tr>
<td>Dialysate flow rate (mL/min)</td>
<td>Autoflow factor of 1.5</td>
<td>500</td>
<td>600</td>
<td>600</td>
</tr>
<tr>
<td>Kt/V urea</td>
<td>1.49 (1.32–1.71)</td>
<td>1.23 ± 0.24</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Administration of fondaparinux</td>
<td>Intravenous</td>
<td>Intravenous</td>
<td>Intravenous</td>
<td>Intravenous</td>
</tr>
<tr>
<td>Predialysis anti-Xa (IU/mL)</td>
<td>0.36 (0.30–0.42)</td>
<td>0.32 ± 0.09</td>
<td>0.04 ± 0.03</td>
<td>0.025 ± 0.025</td>
</tr>
<tr>
<td>Postdialysis anti-Xa (IU/mL)</td>
<td>0.75 (0.65–0.80)</td>
<td>0.89 ± 0.24</td>
<td>0.16 ± 0.04</td>
<td>0.46 ± 0.12</td>
</tr>
</tbody>
</table>

Values are expressed as median (IQR) or as mean ± SD

*aPost-dialysis body weight for all studies except for Ho et al. who did not mention the time of measurement.

*bThe autoflow function automatically regulates the dialysate flow rate, depending on the blood flow rate.

**FIGURE 1:** Illustration of the course of the mean predialysis and postdialysis anti-Xa levels over time. The dots within the brackets represent the mean of all anti-Xa levels measured during the following intervals: Week 0–2, Week 2–4, Week 4–10, Week 10–18 and Week 18–24, whereas the perpendicular lines within the brackets refer to the corresponding 95% confidence intervals during the first 6 months after the introduction of fondaparinux.

pre- and postdialysis anti-Xa levels during the first 6 months. The dots within the brackets represent the mean of all anti-Xa levels measured during the following intervals: Week 0–2, Week 2–4, Week 4–10, Week 10–18 and Week 18–24, whereas the perpendicular lines within the brackets refer to the corresponding 95% confidence intervals. After an initial period of gradually increasing anti-Xa levels due to accumulation of fondaparinux, stable levels were achieved. Haemodialysis without
clotting problems was possible in 96% of the sessions (defined as a semiquantitative clotting score ≤1), whereas two episodes of major clotting (2/459 dialysis sessions) were observed, defined as clotting of the extracorporeal circuit necessitating premature termination of the procedure (Table 2). Two episodes of bleeding from the puncture sites during the dialysis interval were reported in one patient. There were no other cases of bleeding, fondaparinux-associated HIT, cerebrovascular accidents or thromboembolic events. As expected, fondaparinux had no clinically relevant effect on the platelet concentration during the study period (Figure 2).

**DISCUSSION**

In the present observation, the feasibility of treating haemodialysis patients with fondaparinux as a substitute for vitamin K antagonists is described. To the best of our knowledge this idea has never been described nor suggested previously. Patients treated with coumarin were switched to intravenous fondaparinux administered before every haemodialysis session. This resulted in a convenient and effective anticoagulation both during dialysis and the interdialytic interval. Our findings are of clinical importance as coumarin use has been identified as a risk factor for accelerated vascular calcification and calciphylaxis [1–8, 17]. Moreover, taking into account the cost for treatment and monitoring, fondaparinux is predicted to be cost effective compared with conventional treatment with LMWH and vitamin K antagonists. The cost per dialysis session is ± 6.0 euros (2.5 mg fondaparinux + monthly measurement of INR).

Pharmacokinetic data on fondaparinux in healthy persons showed a distribution volume consistent with the extracellular compartment and a renal elimination as unchanged drug with a $T_{1/2} = 17–21\ h$ [24, 25]. In both young and elderly healthy subjects, a once-daily intravenous administration of fondaparinux was sufficient to achieve therapeutic plasma concentrations with a low within- and total-subject variability. Dose proportionality analysis of intravenously administered fondaparinux in this group showed a linear pattern. The excretion and elimination of fondaparinux after repeated administration were similar to those observed after a single dose [24]. However in patients with an impaired kidney function, elimination is slowed, leading to a prolonged half-life [21]. Although safety warnings about its use in renal failure should be taken into account [26], this reduced clearance in renal failure may also be useful to bridge more efficiently the interdialytic interval. Few studies (Table 1) have investigated fondaparinux as an anticoagulant in haemodialysis [27–31]. In 2007, Kalicki et al. [28] compared fondaparinux (0.05 mg/kg) with unfractionated heparin (UFH) in chronic haemodialysis patients. Dialysis anticoagulation was found less successful with fondaparinux compared with UFH. Dialytic removal of fondaparinux by high-flux membranes could be the culprit of premature clotting in that study [28]. Sombolos et al. [29] evaluated the effect of intravenous 2.5 mg fondaparinux in haemodialysis patients using either high-flux or low-flux membranes. High-flux membranes were associated with increased incidence of circuit clotting. On the contrary, in patients dialysed with low-flux dialysers, fondaparinux could be used successfully. These findings point out an enhanced removal of fondaparinux (molecular weight 1728 Da) with high-flux membranes compared with low-flux membranes [29]. In a third report, subcutaneous administration of 2.5 mg fondaparinux before the session was found to be successful and safe in three patients dialysed with high-flux membranes [30]. Due to the potential variable anticoagulant effects in the interdialytic period, it remains a challenge to find the optimum balance between thrombophylaxis efficacy and safety. Taking into account the residual renal function and based on regular measurement of pre- and postdialysis anti-Xa activity levels, it should be possible for the clinician to administer fondaparinux to haemodialysis patients in need of continuous anticoagulation, as also demonstrated in the present study. However, as the data refer to only six patients, it might be useful to obtain confirmation in larger dialysis populations.

We have demonstrated in the present case series that intravenous fondaparinux can be safely used as an alternative to vitamin K antagonists in patients dialysed with low-flux membranes. Efficient anticoagulation was obtained during the

<table>
<thead>
<tr>
<th>Clotting score</th>
<th>% of total haemodialysis sessions ($n = 459$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>Patient 2</td>
</tr>
<tr>
<td>0 = clean filter and no visible clots in drip chambers</td>
<td>89</td>
</tr>
<tr>
<td>1 = some traces of coagulation in filter and/or in drip chambers</td>
<td>10</td>
</tr>
<tr>
<td>2 = a lot of traces of coagulation in filter and/or in drip chambers or presence of a clot</td>
<td>1</td>
</tr>
<tr>
<td>3 = fully clotted extracorporeal system</td>
<td>0</td>
</tr>
</tbody>
</table>
interdialytic interval as well as during all but two sessions. No major bleeding or thromboembolic events were reported. Once steady state was obtained, and in the absence of clinical problems, pre- and postdialysis aXa levels were measured monthly. A careful selection of the patient remains important, weighing up potential benefits and risks. Besides renal failure, fondaparinux is contraindicated in patients with active major bleeding, in patients with a body weight <50 kg undergoing hip fracture, hip replacement or knee replacement surgery and abdominal surgery, in patients with bacterial endocarditis, in patients with thrombocytopenia associated with a positive in vitro test for anti-platelet antibody in the presence of fondaparinux sodium or in patients with known hypersensitivity to fondaparinux sodium [32]. High-flux membranes and haemodiafiltration should be avoided, as they are associated with increased dialytic removal, resulting in enhanced clotting of the circuit, but more importantly, in inadequate anticoagulation during the interdialytic interval. In case of bleeding or planned surgery, haemodiafiltration should be used to increase the clearance of the anticoagulant. In comparison with UFH and LMWHs, which can be totally or partially reversed by the administration of a nonspecific heparin inhibitor (protamine sulphate), there is no specific antidote for fondaparinux at the present time. As the clinical use of protamine sulphate is associated with adverse side effects [33, 34], the development of a specific and effective antidote could be an asset for fondaparinux. Recently, recombinant factor VIIa and a recombinant antithrombin variant (AT-N135Q-Pro394) have been applied as an antidote for fondaparinux [35, 36]. At present, these are however not yet available for routine use. As fondaparinux is not detected by routine anticoagulation tests, it is important to document its use in the medical file and to educate the patient. The limited number of patients in this study restricts the generalization of our findings. A large-scale study is needed to evaluate the long-term effects and to make the comparison with vitamin K antagonists. In conclusion, we found fondaparinux an attractive and easy to use alternative to vitamin K antagonists in haemodialysis patients.

CONFLICT OF INTEREST STATEMENT

None declared.


REFERENCES


FIGURE 2: Illustration of the mean platelet concentration levels over time. The dots within the brackets represent the mean of all platelet concentrations measured during the following intervals: Week 0–2, Week 2–4, Week 4–10, Week 10–18 and Week 18–24, whereas the perpendicular lines within the brackets refer to the corresponding 95% confidence intervals during the first 6 months after the introduction of fondaparinux.


Received for publication: 5.2.2012; Accepted in revised form: 26.5.2013