A single dose of dalteparin effectively prevents clotting during haemodialysis

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Abstract

Background. A single bolus dose of LMW heparin at the start of haemodialysis effectively prevents clot formation in the dialyser and bubble trap. However, there are few studies on the appropriate dosage of LMW heparins in haemodialysis. Therefore we examined the relationship between the anticoagulant effect of dalteparin and clinical clotting during haemodialysis.

Methods. We performed an open, prospective study on 12 haemodialysis patients during a total of 84 sessions (4–4.5 h). The normally applied dose of dalteparin in each patient was reduced by 25% for each session down to 50% of initial dose if no clotting was observed. Clinical clotting (grade 1–4) was evaluated by visual inspection after blood draining of the air trap every hour and by inspection of the dialyser after each session and compared to corresponding values for anti-FXa activity and dialysis time. Blood flow and ultrafiltration rate were kept within narrow limits throughout the study.

Results. No episodes of grade 4 clotting occurred, and no session was interrupted. Eighteen episodes of grade 3 clinical clotting (11%) were observed in patients without warfarin treatment, none with an anti-FXa activity >0.43 IU/ml. Oral warfarin treatment reduced the clinical clotting, and only one grade 3 episode was observed in patients on warfarin therapy. Anti-FXa activity and haemodialysis time were the only factors independently correlated to clotting in a logistic regression model.

Conclusion. An anti-FXa activity above 0.4 IU/ml after 4 h of dialysis inhibits significant clotting during haemodialysis. A bolus dose of dalteparin of 70 IU/kg usually seems appropriate, but may be reduced in patients on warfarin treatment. Dialysis time is an independent risk factor for clinical clotting.

Key words: anti-FXa; anticoagulation; clotting; dalteparin; haemodialysis; single dose

Introduction

Haemodialysis (HD) requires anticoagulation to avoid clotting of the dialyser and extracorporeal circuit. Hitherto, the anticoagulation regimen has consisted of an i.v. bolus dose of unfractionated heparin followed either by i.v. continuous infusion or a new bolus dose during dialysis. However, LMW heparins are being frequently used as they have several potential advantages over unfractionated heparin (UFH) [1,2]. The risk of bleeding is lower than with UFH since LMW heparins interact less with platelets and the vessel wall [3–7]. The risk of heparin-induced thrombocytopenia is also smaller [8]. In addition, the administration is practical, and the effect on the blood lipids may be more favourable [9,10].

We designed this study to assess the relationship between anticoagulant effect of dalteparin and clinical clotting and further to assess the dosage of dalteparin necessary to obtain adequate anticoagulation during HD. Other potential factors that might affect clinical clotting were also evaluated, such as the use of oral anticoagulants and dialysis time. These factors were subjected to multivariate analysis. Extracorporeal blood flow and ultrafiltration rate were kept within narrow limits throughout the study, and Hb and Hct remained unchanged.

Subjects and methods

Patients

Twelve patients, nine men and three women, on chronic HD were included in the study. The primary kidney disease causing chronic renal failure was polycystic kidney disease in four of the patients, AA amyloidosis in two, rapidly progressive glomerulonephritis in one, chronic glomerulonephritis in one, diabetic nephropathy in one, nephrosclerosis in one, reflux nephropathy in one, and Wegener’s granulomatosis in one. Mean age was 60 years (range 26–77 years) and mean body weight was 70 kg (range 51–96 kg). Mean time on HD treatment was 9 months (range 3–17 months). Ten of the patients received erythropoietin at a mean dose 12400 units/week (range 8000–20000).

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Six of the patients were treated with oral warfarin, two because of implanted heart valves (international normalized ratio, INR = 3.3), one because of atrial fibrillation (INR = 2.3), two because of a previously malfunctioning jugular catheter (INR = 1.6), and one because of previous pulmonary embolism and a positive lupus anticoagulant (INR = 2.3). The haemoglobin value was stable, and the dose of erythropoietin and iron supplement were kept unchanged the last 2 weeks prior to the study. Patients receiving acetylsalicylic acid treatment were excluded from the study. Other exclusion criteria were clinical signs of infection and disseminated malignant disease. None of the patients had bleeding disorders. The protocol was approved by the Regional Ethics Committee and informed consent was obtained from all the patients according to the Helsinki declaration.

Dialysis procedure
Dalteparin was given as a single bolus dose into the arterial line at start of dialysis. The mean applied dalteparin dose at the start of the study was 60.9 ± 19.3 IU/kg in the patient group receiving warfarin and 69.5 ± 11.5 IU/kg in those without oral anticoagulation. The dialysis sessions were 4 h three times per week in seven patients and 4.5 or 5 h three times per week in five patients. The dialyser used was F6 HPS, Fresenius, Germany, (polysulphone hollow-fibre filter) for at least 1 week before and during the study. Bicarbonate dialysate was used in all patients. During 1–2 weeks prior to the study (run-in period) the dialyser and the bubble trap were checked at the end of each dialysis session to ensure that there was no clot formation and the dalteparin dose was kept unchanged. The blood flow rate varied between 230 and 300 ml/min, but was kept close to constant within each patient. Blood flow was recorded by the regular dialysis machine flowmeter in the dialysis machine. The dialysate flow was kept constant at 500 ml/min.

Study design
To examine the relationship between anticoagulant effect of dalteparin and intradialytic clinical clotting the dalteparin dose was gradually tapered in subsequent dialysis sessions. A total of 84 HD sessions were studied in 12 patients over a period of 3 weeks in eight patients and 1 week in four patients. The regularly applied dose of dalteparin was given in the first session and then reduced by 25% for each session down to 50% if no clotting was observed. Clinical clotting was evaluated by visual inspection after blood draining of the air trap every hour (1, no clotting in the trap; 2, fibrinous ring; 3, clot formation and 4, coagulated system) and by visual inspection of the dialyser at the end of each session (1, clean filter; 2, a few blood stripes (affecting less than 5% of the fibres seen at the surface of the dialyser); 3, many blood stripes (affecting more than 5% of the fibres) and 4, coagulated filter). If clinical signs of clotting grade 3 or 4 were observed, the dalteparin dose was increased by one step (25% of the initial dose). Clinical clotting was compared to simultaneously measured anti-FXa activity, Hb, Hct, platelet count, blood flow, and ultrafiltration rate.

Blood sampling
Blood specimens were taken from the arterial line after lowering the blood flow to 100 ml/min for 1 min. Hb, Hct, platelets, white cell count, INR, and urea were measured at the start and at the end of the dialysis sessions. Anti-FXa activity was measured after 1, 3 and 4 h in each of the 84 dialysis sessions. Blood for anti-FXa was collected into tubes containing citrate and cooled in an ice-water mix before centrifuging at 4 °C at 2500 g for 30 min.

Laboratory methods
Anti-FXa activity was measured with a chromogenic assay (Coatest®, Chromogenix AB, Mölndal, Sweden).

Statistics
In order to estimate the effect of actual dialysis time and anti-FXa activity on the odds of getting coagulation (defined as clotting grade 2 and 3), a logistic regression model of repeated measurements was adopted (there were several measurements per patient). Since no clotting was found after 1 h only data from 3 and 4 h after the start of dialysis were included in this analysis. SAS version 6.12 (SAS Institute, Cary, NC) was used for the calculations. The relationship between clinical clotting and anti-FXa activity was assessed by one-way analysis of variance by use of one-exponential decay relationship with a computer-based statistical software program, Graph Pad Prism, CA, US. In order to evaluate the relationship between anti-FXa activity and dalteparin dose (IU/kg), a linear regression model was performed (Statistical Software, SPSS). A P value of < 0.05 was consid-
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Table 1. Blood cell parameters during 84 HD sessions in 12 patients (± SD)

<table>
<thead>
<tr>
<th></th>
<th>Haemoglobin (g%)</th>
<th>Haematocrit (%)</th>
<th>Leukocytes (10⁹/l)</th>
<th>Platelets (10⁹/l)</th>
</tr>
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<tbody>
<tr>
<td>Before dialysis</td>
<td>11.5±1.0</td>
<td>35.8±3.6</td>
<td>8.7±3.4</td>
<td>255±89</td>
</tr>
<tr>
<td>After dialysis</td>
<td>12.0±1.3</td>
<td>37.0±4.4</td>
<td>8.4±3.4</td>
<td>260±79</td>
</tr>
<tr>
<td>P-value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

Table 2. Logistic regression model of repeated measurements: results

<table>
<thead>
<tr>
<th></th>
<th>B</th>
<th>SE</th>
<th>P-value</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time</td>
<td>1.17</td>
<td>0.29</td>
<td>&lt;0.0001</td>
<td>3.229</td>
</tr>
<tr>
<td>Anti-FXa</td>
<td>−3.75</td>
<td>1.00</td>
<td>0.0003</td>
<td>0.0235</td>
</tr>
</tbody>
</table>

Discussion

We found that a single dose of dalteparin effectively inhibited significant coagulation in the bubble trap or dialyser without interruption of any of the 84 dialysis sessions. This was true even when the doses were reduced down to 50% of those conventionally applied. Not surprisingly, a significant correlation was found...
Fig. 2. The correlation between dalteparin dose and anti-FXa activity (IE/ml) in 12 patients receiving different doses of dalteparin. The continuous line is the regression line for anti-FXa activity after 4 h of dialysis, and the broken line shows the calculated anti-FXa levels after 5 h. Since anti-FXa activity after 4 h of dialysis should be more than 0.4 IU/ml (lower in patients receiving warfarin) the adequate dalteparin dose is given by the curve. Taking the inter-patient variability into consideration, a safety margin of up to 50% may be applicable.

For anti-FXa values under the detection limit (0.1 IU/ml) a value was estimated assuming a first-order decline. Since time is an independent factor for clotting, the dose of dalteparin should probably be higher than indicated for 5-h dialysis sessions.

between the degree of intradialytic clinical clotting and the anticoagulant effect measured as anti-FXa activity (Figure 1). The risk of major clotting events was close to zero with an anti-FXa level higher than 0.4 IU/ml after 4 h of dialysis. This is in agreement with other studies on LMW heparins in haemodialysis [13]. Obviously, major clot formations should be avoided since the dialysis session may be interrupted and the patient may suffer unnecessary blood loss.

The individual effects of dialysis time and anticoagulant effect may be difficult to assess since an increase in dialysis time is accompanied by reduced anticoagulant effect from a single initial dalteparin dose. Nevertheless, using a logistic regression model of repeated measurements we revealed that dialysis time is an independent risk factor for clinical clotting during haemodialysis. This finding may not be surprising but has not been positively demonstrated by previous studies.

The aim of this study was to relate dalteparin dosage to clinical clotting. Traditionally the dose is arbitrarily chosen according to clinical experience. We found a highly significant linear relationship between anti-FXa level after 4 h of dialysis and dalteparin dose (Figure 2). An estimate of the dose needed to avoid significant clinical clotting can be made from this plot. Because of the great biologically interindividual variance in the anticoagulant activity (dalteparin) elimination half-life, up to 50% may be added to the estimated dose to ensure a level of at least 0.4 IU/ml at the end of a 4 h dialysis session. With an added safety margin of 50% to the calculated dose, the recommendation will be about 5000 IU dalteparin for a 4 h session in a patient weighing 70 kg. Alternatively, the actual anti-FXa activity level may be measured after 4 h and the dose adjusted if necessary.

A standard polysulphone dialyser (Fresenius F6) was used in all sessions in this study. Since dalteparin is removed by dialysis the clearance of small molecules of the dialyser may be of importance. High-clearance filters may remove dalteparin at a higher rate and result in a more rapid decrease in anticoagulant effect over time. Also variation in ‘biocompatibility’ between different dialysers may modify the anticoagulant effect. However, such mechanisms could not be elucidated in our study. The elimination half-life of dalteparin averaged 2.2 ± 0.9 h during haemodialysis. Interestingly, this is in agreement with the half-life of dalteparin given i.v. to healthy people without renal failure [12].

It is well known that oral anticoagulant treatment may prevent thrombosis in central venous catheters, including dialysis catheters [14,15]. Obviously, oral anticoagulant treatment may also reduce clinical clotting episodes during haemodialysis, but to our knowledge such an effect has not previously been examined in dialysis patients. In the present study treatment with oral warfarin had a major impact on the degree of clinical clotting episodes. The mean INR for the six patients receiving warfarin was 2.2, indicating that a moderate anticoagulation protects against clotting during haemodialysis. Actually, the patients treated with warfarin were in need of a very low dose of dalteparin. In general, anti-FXa activity at the lowest detection level at the end of dialysis was sufficient to avoid severe clotting in these patients. This may have clinical relevance since many of the dialysis patients
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are treated with warfarin for cardiovascular comorbidity [16,17].

Extracorporal blood flow and ultrafiltration rate may also be factors influencing clinical coagulation. In the present study these factors were kept within narrow limits, and Hb, Hct, and platelet count remained virtually unchanged throughout the study. Therefore any correlation between these factors and clinical clotting cannot be assessed by the present study.

In conclusion, we found that a single dose of dalteparin effectively inhibits significant clotting for at least 4 h during haemodialysis. Clinical clotting is correlated to anticoagulant effect and is avoided with an anti-FXa activity above 0.4 IU/ml at the end of a 4 h dialysis session. This is normally obtained with an initial bolus dose of dalteparin of about 70 IU/kg. Our data also show that the dose of dalteparin may be reduced with simultaneous oral warfarin treatment, and that time of dialysis is an independent variable for clinical clotting.

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References


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