A single bolus of a low molecular weight heparin to patients on haemodialysis depletes lipoprotein lipase stores and retards triglyceride clearing

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Abstract

Background. Low molecular weight heparins (LMWH) are increasingly used during haemodialysis (HD) to prevent clotting in the extracorporeal devices. It has been suggested that LMWH release endothelial-bound lipoprotein lipase (LPL) less efficiently than unfractionated heparin (UFH) does and thereby cause less disturbance of lipid metabolism. Evidence from in vitro studies and from animal experiments indicate, however, that both types of heparin preparations have the same ability to release endothelial LPL, but LMWH are less effective in preventing uptake and degradation of LPL in the liver. Model studies in humans indicate that LMWH cause as much depletion of LPL stores and impaired lipolysis of triglyceride (TG)-rich lipoproteins as UFH does.

Methods. Two anticoagulant regimes based on present clinical practice were compared in nine HD patients. UFH was administered as a primed infusion, whereas the LMWH (dalteparin) was given only as a single bolus pre-dialysis. Blood was sampled regularly for LPL activity and TG.

Results. LPL activity in blood was significantly lower during the dialysis with dalteparin. To explore the remaining activity at the endothelium, a bolus of UFH was given only as a single bolus pre-dialysis. Blood was sampled regularly for LPL activity and TG.

Conclusions. This study indicates that a single bolus of dalteparin pre-dialysis interferes with the LPL system as much as, or more than an infusion of UFH does.

Keywords: dalteparin; dialysis; heparin; lipoprotein lipase; low molecular weight heparins

Introduction

During haemodialysis (HD), anticoagulation is used to prevent clotting of the dialyser and extracorporeal circuit. Unfractionated heparin (UFH) has been in widespread use for decades and is usually given as a primed infusion. UFH releases endothelial-bound lipoprotein lipase (LPL), the major enzyme responsible for hydrolysing triglycerides (TG) in circulating lipoproteins [1]. It has been suggested that repeated exposure to UFH may result in a depletion of tissue LPL stores and may thereby contribute to the hypertriglyceridaemia in HD patients [2]. For some years, various low molecular weight heparins (LMWH) have been developed progressively for use in extracorporeal circuits and advocated as principal anticoagulant agents for routine HD rather than UFH [3]. LMWH are suggested to release endothelial-bound LPL less efficiently and thereby cause less derangement of lipid metabolism compared with UFH [4].

Recently, we infused UFH [5] and a LMWH (dalteparin) [6] to healthy controls to explore the influence on LPL activity and TG response. There was an initial peak of LPL activity as well as a reduction in TG during the first hour. Then, LPL decreased towards a plateau, while TG increased towards and beyond the baseline. During the infusion of dalteparin, both the peak and the plateau activities of LPL were reduced to almost one-third of the activities during the corresponding infusion of UFH. A bolus of UFH given when the LPL activity had levelled off to a plateau brought out about the same amount of activity, regardless of whether dalteparin or UFH had been infused. The conclusion was that both heparin
preparations had reduced the peripheral stores of LPL to a similar extent and that the difference in plasma levels of LPL activity was due to a more rapid hepatic clearance of the LPL–dalteparin complex. There was a tendency towards a more pronounced increase in TG during the dalteparin infusion compared with UFH.

Previous studies had shown that when an infusion of UFH was used as anticoagulant to HD patients during dialysis, the peak of LPL activity was only half of that in the controls, while the plateau was comparable [7]. Our interpretation was that the functional pool of LPL activity, represented by the initial peak, was impaired in HD patients while the production of lipase molecules, reflected by the plateau, was only marginally reduced. When dalteparin was infused during dialysis, both the peak and the plateau levels of plasma LPL activity were only about one-third of the activities during the corresponding dialysis with UFH. There was no initial decrease in TG and the subsequent increase in TG was marked and more pronounced [8]. This indicated to us that dalteparin had caused a profound depletion of the peripheral stores of LPL and that lipoprotein metabolism might be more, rather than less, disturbed by an infusion of dalteparin than of UFH. Various LMWH are used routinely during dialysis in many centres. The LMWH preparations are usually administered as a single bolus at start. To explore the influence of this new procedure on LPL activity and TG, two anticoagulant regimes based on clinical practice were compared, following the respective manufacturer’s recommendations. UFH was administered as a primed infusion, whereas dalteparin was given as a single bolus at start, not followed by an infusion.

Subjects and methods

Patients

The study included nine HD patients, four females and five males (Table 1). The median age was 72 years (range: 27–85 years) and the median body mass index (BMI) was 26 kg/m² (range: 19–31 kg/m²). The diagnosis of renal failure was chronic glomerulonephritis, nephrosclerosis, polycystic kidney disease, multiple myeloma in remission, medullary sponge kidney and end-stage kidney disease. The patients were treated with antihypertensive drugs (angiotensin-converting enzyme inhibitors, calcium channel inhibitors, beta-blockers), diuretics, sodium bicarbonates and calcium-based phosphate-binding drugs. All received erythropoietin. No one was treated with lipid-lowering drugs and none received warfarin or other vitamin K antagonists. They had been on chronic HD for 4–40 months and all received UFH as anticoagulant in their regular HD sessions. All had an arteriovenous (AV) fistula/graft as dialysis access. No one displayed any overt signs of infection or inflammation (C-reactive protein <10 mg/l). None of the patients had participated in our earlier studies [5–8]. The local ethical committee approved the study, and both oral and written information was given before signed consent was obtained from all patients prior to participation.

Dialysis procedure

The patients were treated with bicarbonate HD either two or three times weekly. The dialysis dose was estimated using weekly Kt/V for urea and varied between 1.27 and 1.97 with a median value of 1.45. Eight patients had polysulphone dialysers (F8HPS; Fresenius, Bad Homburg, Germany) and one used a polyamide dialyser (PF14s; Gambro, Lund, Sweden). The dialysers were primed with saline without heparin. All dialyses were performed with Biosol dialysis solution (Pharmalink, Stockholm, Sweden). The experiments were carried out after an overnight fast and 48–72 h had passed since the previous HD. The patients were given breakfast ~2 h after start of dialysis and lunch was served when the dialysis was completed, i.e. after 4 h. The meals were standardized during both dialyses and included 15 E% protein, 55 E% carbohydrates and 30 E% fat.

Study protocol

Two anticoagulation regimes based on present clinical practice were compared and the doses were adjusted to the respective manufacturer’s recommendation. The first was with UFH (Leo Pharma, Malmö, Sweden) as anticoagulant. The second (2 weeks later) was with a LMWH, dalteparin (Pharmacia, Stockholm, Sweden). The UFH dose for each patient was based on the dosing schedule previously established during the individual’s regular dialysis-sessions.

<p>| Table 1. Basic characteristics for the study subjects and lipid values prior to dialysis with UFH. Values in brackets are prior to dialysis with dalteparin |</p>
<table>
<thead>
<tr>
<th>HD Patients</th>
<th>Age (years)</th>
<th>Gender</th>
<th>Weight (kg)</th>
<th>BMI (kg/m²)</th>
<th>TG (mmol/l)</th>
<th>Cholesterol (mmol/l)</th>
<th>HDL (mmol/l)</th>
<th>LDL (mmol/l)</th>
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<tr>
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<td>38</td>
<td>Female</td>
<td>50</td>
<td>19</td>
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<td>5.8 (5.7)</td>
<td>2.09 (2.08)</td>
<td>3.2 (2.9)</td>
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<td>2</td>
<td>48</td>
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<td>85</td>
<td>31</td>
<td>2.24 (1.62)</td>
<td>6.1 (5.7)</td>
<td>0.72 (0.76)</td>
<td>4.4 (4.2)</td>
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<tr>
<td>3</td>
<td>72</td>
<td>Female</td>
<td>67</td>
<td>26</td>
<td>1.53 (1.59)</td>
<td>5.1 (4.8)</td>
<td>2.13 (1.96)</td>
<td>2.3 (2.1)</td>
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<tr>
<td>4</td>
<td>76</td>
<td>Female</td>
<td>58</td>
<td>23</td>
<td>1.05 (1.60)</td>
<td>4.4 (4.6)</td>
<td>1.39 (1.17)</td>
<td>2.6 (2.7)</td>
</tr>
<tr>
<td>5</td>
<td>27</td>
<td>Male</td>
<td>65</td>
<td>22</td>
<td>2.09 (1.44)</td>
<td>3.8 (4.4)</td>
<td>0.64 (0.84)</td>
<td>2.3 (2.9)</td>
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<tr>
<td>6</td>
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<td>1.36 (1.20)</td>
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<td>23</td>
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<td>4.8 (5.0)</td>
<td>1.01 (1.14)</td>
<td>3.0 (2.8)</td>
</tr>
<tr>
<td>8</td>
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<td>27</td>
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<td>3.2 (3.5)</td>
<td>1.24 (1.21)</td>
<td>1.6 (1.8)</td>
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<tr>
<td>9</td>
<td>85</td>
<td>Male</td>
<td>80</td>
<td>28</td>
<td>0.91 (1.00)</td>
<td>4.8 (5.2)</td>
<td>1.25 (1.44)</td>
<td>3.2 (3.3)</td>
</tr>
<tr>
<td>Median values</td>
<td>1.53 (1.59)</td>
<td>4.8 (5.0)</td>
<td>1.25 (1.20)</td>
<td>3.0 (2.9)</td>
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</table>
i.e. a loading dose of ~50 IU/kg body weight, followed by a continuous infusion of 800–1500 IU/h. The infusion was discontinued ~30 min prior to cessation of dialysis in order to prevent bleeding from the AV fistulas after dialysis. Dalteparin was administered according to the manufacturer’s recommendation for Sweden, i.e. a single bolus dose of 5000 IU to all patients at start of dialysis, not followed by an infusion. This corresponded to a median of 72 IU/kg body weight (range: 59–100 IU/kg body weight). All dialyses were completed after 4 h. Blood samples for lipids, LPL and hepatic lipase (HL) were drawn at start and at 15, 30, 60, 180 and 240 min. Further samples for lipids were drawn at 7, 8, 10, 24 and 48 h. The anticoagulation effect during the dialyses was evaluated by activated partial thromboplastin time (APTT) and antifactor Xa activity. At a later occasion, eight of the patients participated in two further dialyses each, using UFH and dalteparin, respectively. The heparin preparations were administered as during the first session for the first 3 h. Then, at 180 min, a blood sample was taken for assay of lipase activities and a bolus of UFH (251 IU/kg body weight) was given to release remaining LPL into the circulating blood. After that, no more of the heparin preparations were infused. Blood samples were taken at 195, 210 and 240 min. Everything else concerning the dialysis regimen was unchanged between the dialyses. The medical treatment and diet recommendations were kept constant.

**Laboratory methods**

Blood samples were collected in heparinized tubes for measurement of LPL and HL activity and LPL protein mass by the same methods as used in earlier studies [5–8]. They were chilled immediately in ice water and centrifuged within 15 min in a cooling centrifuge. The plasma was frozen at −20°C and then stored at −70°C until analysis. For HL, we used a gum arabic-stabilized emulsion of triolein containing [3H]oleic acid-labelled triolein. The incubation medium included 1 mol/l NaCl. Under these conditions, LPL is inactivated. LPL activity was measured with an emulsion containing, per millilitre, 10 mg egg-yolk phospholipids, 100 mg soybean TG and a trace amount of [1H]oleic acid-labelled triolein. This emulsion was prepared by Fresenius-Kabi (Uppsala, Sweden). For the LPL assay, HL activity was inhibited by pre-incubation of the samples with immunoglobulins from a rabbit antiserum to human HL. The LPL assay medium contained a relatively high concentration of heparin and differences in the heparin concentration or preparations was low and did not differ between the

then frozen as described above. Total cholesterol, high-density lipoprotein (HDL) cholesterol and TG were determined by routine methods on a multianalyser (Vitros 950 IRC; Johnson & Johnson Clinical Diagnostics Inc., New York, NY, USA). The levels of low-density lipoprotein (LDL) cholesterol were calculated with the Friedewald formula.

Blood drawn in citrate-containing tubes was analysed for APTT by routine methods. Antifactor Xa activity was determined with a chromogenic substrate (Coacute; Chromogenix AB, Malmö, Sweden).

**Statistical analysis**

Data are expressed in terms of median and range. Paired analyses were performed for significant differences using the Wilcoxon signed rank test. The Spearman rank correlation test was used to evaluate relationships between variables. Two-tailed P-values of <0.05 were considered statistically significant.

**Results**

**Baseline data**

Data for the patients at the time of the first (UFH) dialysis are given in Table 1. There was no significant difference between the two dialyses for any of the parameters. The respective median values before the UFH and dalteparin dialyses, respectively, were TG 1.53 mmol/l (range: 0.81–2.24 mmol/l) and 1.59 mmol/l (range: 1.00–2.64 mmol/l), total cholesterol 4.8 mmol/l (range: 3.2–6.1 mmol/l) and 5.0 mmol/l (range: 3.5–5.7 mmol/l), HDL cholesterol 1.25 mmol/l (range: 0.64–2.13 mmol/l) and 1.20 mmol/l (range: 0.76–2.08 mmol/l), and LDL cholesterol 3.0 mmol/l (range: 1.6–4.4 mmol/l) and 2.9 mmol/l (range: 1.8–4.2 mmol/l). There was no significant difference between the ultrafiltration rates during the two dialyses.

**Anticoagulation effect**

During dialysis with UFH, the APTT values ranged between 43 and 86 s, i.e. all patients had a prolongation of the APTT to 150% of their pre-dialysis values, as recommended [3,10]. During dialysis with dalteparin, the antifactor Xa activity varied between 0.81 and 1.98 IU/ml in samples taken at 15 and 30 min after the administration of dalteparin. At 240 min, the activity had decreased to a median of 0.39 IU/ml (range: 0.24–0.74 IU/ml). Five patients had an antifactor Xa activity of <0.40 IU/ml at the end of dialysis. There was no correlation between the amount of dalteparin given per kg body weight and the antifactor Xa activity at any of the time points. No coagulation of the dialysate blood circuit could be detected visually in any of the dialyses.

**LPL activity in blood**

LPL activity prior to administration of the heparin preparations was low and did not differ between the
two dialyses. The median value was 0.60 mU/ml (range: 0.32–3.44 mU/ml) before UFH and 0.84 mU/ml (range: 0.31–1.18 mU/ml) before dalteparin. When the heparin preparations were injected and the dialyses were started, LPL activity increased and peaked at 15 or 30 min (Figure 1). During dialysis with UFH, the median activity was 84 mU/ml (range: 53–144 mU/ml) at 15 min and 76 mU/ml (range: 59–163 mU/ml) at 30 min. The corresponding values for the dialyses with dalteparin were 66 mU/ml (range: 51–113 mU/ml) and 62 mU/ml (range: 45–111 mU/ml). These values were not significantly different comparing UFH and dalteparin. After 30 min, the activity decreased rather sharply. During the dialysis with UFH, the LPL activity was 22 mU/ml (range: 9–43 mU/ml) at 180 min. The activity then fell to 11 mU/ml (range: 6–35 mU/ml) at 240 min. The rapid decrease during the last hour is probably explained by a decrease in the concentration of UFH in blood, as the infusion, following clinical routines, was stopped after ~3.5 h to prevent bleeding from the AV fistulas after dialysis. During the dialysis with dalteparin, the LPL activity was 6 mU/ml (range: 4–15 mU/ml) at 180 min and 5 mU/ml (range: 1–10 mU/ml) at 240 min. These levels were significantly lower than those during dialysis with UFH (P < 0.01). The median area under the curve (AUC) for LPL activity was calculated. AUC during the peak (0–60 min) for the dialysis with dalteparin corresponded to 80% of AUC for the dialysis with UFH. This difference, 2997 mU/ml × 60 min (range: 2126–4939) vs 3660 mU/ml × 60 min (range: 2623–7534), was not statistically significant. During the plateau (180–240 min), AUC with dalteparin was only 30% of that with UFH (P < 0.01): 334 mU/ml × 60 min (range: 152–762) vs 1076 mU/ml × 60 min (range: 545–2334). The peak LPL activities (at 15, 30 and 60 min) for each individual patient correlated positively with each other, both during the dialysis with UFH (P < 0.01) and during the dialysis with dalteparin (P < 0.05). The plateau activities (180 and 240 min) correlated positively with each other during the dialysis with dalteparin (P < 0.01) and tended to correlate during the dialysis with UFH. There was no association between the activities during the peak and the plateau in any of the dialyses.

To explore how much lipase activity remained at the endothelium, a bolus of UFH was given at 180 min, i.e. 1 h before the dialyses were completed. In both dialyses, the bolus caused an increase of the LPL activity, but the second peak was much lower than the initial peak (P < 0.05; Figure 2). The peak values were similar for the dialyses with UFH and with dalteparin, but the increase in activity from 180 min to the peak value was significantly higher in the dialysis with dalteparin, because the activity before the bolus was lower than in the dialysis with UFH. AUC for the peak after the bolus did not differ between the two dialyses.

**LPL mass in blood**

Substantial amounts of LPL mass were noted in the basal samples. These levels did not differ between the two dialyses. The median value was 49 ng/ml (range: 28–130 ng/ml) before dialysis with UFH and 57 ng/ml (range: 26–102 ng/ml) before dialysis with dalteparin. When the dialyses were started, LPL mass increased and the pattern then followed closely that of LPL activity. The increase in LPL mass correlated positively with the increase in LPL activity throughout both dialyses and this correlation was statistically significant for all times (P < 0.05), except at 180 min during the dialysis with dalteparin. No correlation was found between the level of LPL mass before dialysis and the increase in mass during any of the dialyses. There was no association between LPL mass and LPL activity prior to start in any of the dialyses. To calculate the specific activity (LPL activity/LPL mass), the basal value was subtracted from the values obtained during dialysis. The specific activity for the peak values (15 and 30 min) ranged between 0.20 and 0.24 mU/ng, and did not differ between the two dialyses. This indicates that both heparin preparations released the same form of the enzyme and that the difference between UFH and
dalteparin was not due to a difference in ability to keep the lipase in its active form, but more likely due to a different influence on the turnover of the lipase.

**HL activity in blood**

HL activity prior to administration of the heparin preparations was low and did not differ between the two dialyses. The median value was 1.32 mU/ml (range: 0.37–4.24 mU/ml) before UFH and 0.96 mU/ml (range: 0.29–2.54 mU/ml) before dalteparin. When the dialyses were started, HL activity increased and reached a peak at 15 or 30 min (Figure 3). During dialysis with UFH, the median HL activity was 189 mU/ml (range: 83–354 mU/ml) at 15 min and 214 mU/ml (range: 79–340 mU/ml) at 30 min. The corresponding values for the dialysis with dalteparin were 173 mU/ml (range: 57–255 mU/ml) and 152 mU/ml (range: 49–218 mU/ml), respectively. During dialysis with UFH the activity remained high until 180 min (median: 167 mU/ml; range: 42–222 mU/ml), but then decreased to 92 mU/ml (range: 27–173 mU/ml) at 240 min. This decrease is probably explained by the decrease of the concentration of UFH in blood, as the infusion was stopped after ~3.5 h to prevent bleeding from the AV fistulas after dialysis. During the dialysis with dalteparin, HL activity decreased rather sharply after 30 min and reached 21 mU/ml (range: 5–59 mU/ml) at 180 min and 11 mU/ml (range: 1–36 mU/ml) at 240 min. The activity was significantly lower during the dialysis with dalteparin compared with the dialysis with UFH ($P<0.05$), except at 15 min. The median AUC during 0–240 min in mU/ml × 240 min for the dialysis with dalteparin corresponded to 35% of that for the dialysis with UFH (median: 15 112, range: 47 55–28 419 vs median: 41 679, range: 14 209–58 224; $P<0.01$). In both dialyses, the HL activities for each individual patient tended to correlate with each other and this was statistically significant ($P<0.05$), except for the 15 min value compared with the 180 and 240 min values during the dialysis with dalteparin. No correlation was found between HL and LPL activities in any of the dialyses.

After the bolus of UFH at 180 min, HL activity increased to a second peak in both dialyses (Figure 4). The peak value after the bolus was significantly higher than the initial peak during the dialysis with dalteparin ($P<0.05$), but not during the dialysis with UFH. AUC for the peak after the bolus did not differ between the two dialyses.

**Triglycerides**

TG decreased during the first hour in both dialyses, then began to increase and reached values higher than baseline (Figure 5). The lowest values were at 60 min, when the reduction was 40% during dialysis with UFH and 30% during dialysis with dalteparin ($P<0.05$), but not during the dialysis with UFH. AUC for the peak after the bolus did not differ between the two dialyses.

The changes in TG during the observation time were compared between the two dialyses. The increase from baseline to 240 min was significantly higher during the dialysis with dalteparin ($P<0.05$). The median value
was 1.59 mmol/l (range: 1.00–2.64 mmol/l) at start and increased to 2.12 mmol/l (range: 1.45–2.77 mmol/l) at 240 min. The corresponding values during dialysis with UFH were 1.53 mmol/l (range: 0.81–2.24 mmol/l) and 1.51 mmol/l (range: 1.14–3.78 mmol/l). The changes in TG at the other time-points did not differ between the two dialyses. The maximal TG values were reached at 7 h (median: 2.25 mmol/l; range: 1.47–4.79 mmol/l) after the dialysis with UFH and 2.42 mmol/l (range: 1.35–4.37 mmol/l) after the dialysis with dalteparin. At 10 h, TG values had decreased to 1.81 mmol/l (range: 1.34–3.23 mmol/l) for the dialysis with UFH and to 1.91 mmol/l (range: 1.15–3.18 mmol/l) for the dialysis with dalteparin. At 24 h, TG was 1.56 mmol/l (range: 1.10–2.93 mmol/l) and at 48 h it was 1.40 mmol/l (range: 0.89–2.62 mmol/l) after dialysis with UFH. Corresponding values after dialysis with dalteparin were 1.83 mmol/l (range: 1.07–2.62 mmol/l) and 1.58 mmol/l (range: 1.09–2.56 mmol/l). No correlation was found between the changes in TG, LPL and HL activities in any of the dialyses.

**Cholesterol**

Only small changes occurred in total cholesterol and LDL cholesterol, and there were no statistically significant differences between the two dialyses. HDL cholesterol increased from 1.25 mmol/l (range: 0.64–2.13 mmol/l) at start to 1.42 mmol/l (range: 0.80–2.30 mmol/l) at 24 h when UFH was used during dialysis. Corresponding values for the dialysis with dalteparin were 1.20 mmol/l (range: 0.76–2.08 mmol/l) and 1.37 mmol/l (range: 0.79–2.10 mmol/l). The increase was significantly higher during the dialysis with UFH compared with the dialysis with dalteparin ($P < 0.05$).

**Discussion**

The purpose of this study was to explore the influence of two different anticoagulant regimes on LPL activity and TG values in HD patients during dialysis. UFH and a LMWH (dalteparin) were used and the doses were adjusted to the respective manufacturer’s recommendation. The results indicate that, in this clinical setting, dalteparin depletes LPL stores at least as efficiently as UFH does. Both regimes temporarily retard the metabolism of TG-rich lipoproteins, dalteparin somewhat more than UFH.

It is not obvious how one should compare doses of UFH and LMWH preparations, since they differ both in their pharmacokinetic properties and in their mechanism of action [11]. Our comparisons are based on clinical doses, as recommended from manufacturers and clinical guidelines for HD, not on a molecule-for-molecule basis.

The pharmacodynamics of UFH varies widely between patients [11] and this makes an individual dosing schedule necessary. For routine anticoagulation with UFH during HD, the usual recommendation is a loading dose of ~50 IU/kg body weight, followed by a continuous infusion of 800–1500 IU/h [3], or a slightly lower loading dose, 25–30 IU/kg body weight, followed by infusion of 1500–2000 IU/h [10]. It is essential to evaluate the anticoagulant effect by measuring the time taken for clot formation. Traditionally, APTT is used and a prolongation to 150% of the pre-dialysis value is recommended [3,10]. In our study, all patients fulfilled this criterion, indicating adequate anticoagulation for HD. As LMWH preparations have longer duration of the anticoagulant effect [11], a single bolus injection pre-dialysis is now often advocated [12]; also in dialysis sessions of 5 h duration [13]. For dalteparin, the manufacturer recommends a single dose of 5000 IU, irrespective of the body weight. We followed that recommendation. In five of our patients, the antifactor Xa activity was <0.41 IU/ml at the end of dialysis, i.e. values below what is recommended [10]. This indicates that one should check that sufficient anticoagulation is maintained also when using LMWH as anticoagulant, especially in dialysis sessions of >4 h. It is important to stress that clinical findings associated with a given LMWH preparation cannot be extrapolated to another preparation or generalized to the whole LMWH family [11].

Animal experiments indicate that LMWH or decasaccharides release LPL from extrahepatic tissues as efficiently as UFH does [14], but that they do not impede hepatic uptake and degradation of the enzyme to the same extent [15]. Our data are in accord with this. The plasma LPL activities were comparable during the first hour in the two dialyses, but the subsequent decrease was more pronounced during dialysis with dalteparin. During the last hour, the activity was only 30% of that during the dialysis with UFH. This was probably because the concentrations of dalteparin decreased with time after the single bolus, whereas the UFH concentrations were maintained by the infusion.

A bolus of UFH after 180 min brought out a somewhat larger amount of LPL activity during the dialysis with dalteparin, indicating that slightly more LPL remained at the endothelium. On the other hand, the accumulated LPL activity after the bolus did not differ between the two dialyses. This indicates that as much LPL had been cleared by the liver during the preceding 3 h of dialysis with both heparin preparations.

Similar amounts of HL activity appeared in blood after dalteparin as after UFH. After the initial peak, the activity remained essentially unchanged during the dialysis with UFH, but decreased with time during the dialysis with dalteparin. This was probably a consequence of the decreasing concentration of dalteparin, rather than due to any large difference in the ability of dalteparin to release HL compared with UFH. This conclusion is in concert with the results of Chevreuil et al. [16], who found, in rats, that a LMWH released HL as efficiently as UFH did. In further support of this conclusion, the decrease in HL activity in our study
correlated with the decrease in antifactor Xa activity during the later part of the dialysis. Thus, the different patterns of HL activity in blood probably reflect the fact that dalteparin was given as a bolus and its concentration decreased with time whereas UFH was infused. In concert with this interpretation, the HL activity decreased during the last hour of the UFH dialysis, when the infusion of UFH was stopped. When a bolus of UFH was given after 3 h of dialysis, the HL activity increased again and reached values as high, or higher, than during the first peak. Hence, the total amount of accessible HL in the system was essentially unchanged and it appears that the level of the heparin preparations in blood determined the distribution of HL between binding sites in the liver and the circulating blood. In contrast to the effects of the heparins on LPL, the heparins did not seem to have any major consequences for the turnover of HL. It is not known if the redistribution of HL from liver to blood has any effects on lipoprotein metabolism.

TG decreased during the first hour of the dialyses and then increased again. The initial decrease was less marked, but the subsequent increase was more pronounced with dalteparin than with UFH. The decrease in TG is a logical consequence of the displacement of LPL into the circulating blood where the enzyme has ready access to the lipoproteins. That the decrease in TG was less pronounced during dialysis with dalteparin is in concert with the lower levels of circulating LPL. The increase of TG in the later part of the dialyses indicated that the LPL stores had been exhausted and that the total amount of LPL available for lipoprotein metabolism was critically low [6–8]. A reduced capacity to hydrolyse TG during a period after heparin injection has been observed in animal experiments [17]. Our present data indicate that the depletion of LPL was as large as, or larger, with dalteparin than with UFH. This is in line with earlier observations [6] and animal experiments [16,17]. Persson [4] made observations that lend themselves to a similar interpretation; that investigation infused a lipid emulsion to normal subjects. When the TG had established a steady level, dalteparin or UFH was injected. The TG level decreased promptly but in the dalteparin group, it started to rise again and after ~2 h the TG exceeded the level established before the heparin preparations were given.

A number of studies in HD patients have reported that during chronic administration of heparin, e.g. in conjunction with dialyses, the use of a LMWH results in a more favourable plasma lipid profile compared with UFH [18], but conflicting results exist [19]. In contrast to most other studies, we analysed TG variations during and after a dialysis session. Our data indicate that TG clearance was as much or even more, not less, disturbed during dialysis with dalteparin in comparison to UFH. This implies that during some hours at the end of and after the dialysis session there is an increased number of partially metabolized chylomicrons and/or very low-density lipoprotein remnants in the blood. The nature and composition of the accumulating lipoproteins was not analysed in this study. It is of interest to note that a defect in the hepatic clearance of postprandial lipoproteins has been reported in HD patients. On basis of this, it has been suggested that elevated concentrations of remnant lipoproteins may be an important pathogenic factor in the accelerated atherosclerosis seen in HD patients [20]. These data, and our current observations, raise the question if accumulation of atherogenic remnant particles during dialysis with heparin may accelerate atherosclerosis.

In conclusion, this study indicates that a single bolus of dalteparin pre-dialysis interferes with the LPL system as much or more than an infusion of UFH does. Both heparin preparations have the same ability to release endothelial LPL, but dalteparin is less effective in preventing uptake of LPL by the liver. As a result, the depletion of LPL stores and the temporarily impaired lipolysis of TG-rich lipoproteins were as large or even larger using the anticoagulation protocol with a single bolus of dalteparin compared with the traditional protocol with infusion of UFH.

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References

after heparin are separate parameters with different relations to plasma lipoproteins. *Arterioscler Thromb Vasc Biol* 1995; 15: 1086–1093


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