Pharmacokinetic Studies of Dalteparin (Fragmin), Enoxaparin (Clexane), and Danaparoid Sodium (Orgaran) in Stable Chronic Hemodialysis Patients

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• ***Background:*** **Low molecular weight heparins (LMWHs) and danaparoid are an alternative to unfractionated heparin (UH) for anticoagulation during hemodialysis. Few data are available concerning their duration of action and whether drug accumulation occurs with continued use. We performed a prospective randomized study of the pharmacokinetics of dalteparin and enoxaparin plus danaparoid in 21 hemodialysis patients.** ***Methods:*** **Patients were randomly assigned to administration of enoxaparin, 40 mg; dalteparin, 2,500 U; or danaparoid, 34 U/kg, for 4 weeks. Antifactor Xa levels were measured at the end of weeks 1 and 4 immediately before the injection and at prescribed intervals up to 48 hours postinjection.** ***Results:*** **No bleeding or thrombotic episodes occurred during the study. Mean antifactor Xa activities 4 hours postinjection were 0.2 ± 0.035 (SEM), 0.38 ± 0.028, and 0.54 ± 0.051 U/mL week 1 and 0.26 ± 0.038, 0.40 ± 0.055, and 0.64 ± 0.050 U/mL week 4 for dalteparin, enoxaparin, and danaparoid, respectively. Both weeks 1 and 4, antifactor Xa activity 3 hours postdose was significantly greater for danaparoid sodium compared with enoxaparin and dalteparin. There were no significant differences between antifactor Xa activity week 4 versus week 1 for enoxaparin and dalteparin; however, danaparoid sodium levels during dialysis were significantly greater after 4 weeks of treatment (*** $P = 0.0328$ **, 1 hour;** $P = 0.003$ **, 2 hours;** $P = 0.0128$ **, 3 and 4 hours).** ***Conclusion:*** **Dalteparin and enoxaparin provide adequate anticoagulation for hemodialysis using single bolus injections at relatively low doses. Danaparoid sodium at the current recommended dosage resulted in greater anticoagulation than enoxaparin or dalteparin and may have an accumulative effect on anticoagulation with continued treatment.** ***Am J Kidney Dis*** **40:990-995.**

INDEX WORDS: Hemodialysis (HD); anticoagulation; danaparoid sodium; low molecular weight heparin (LMWH); pharmacokinetics.

UNFRACTIONATED heparin (UH) delivered as a bolus and then through a constant infusion is the most commonly used method of anticoagulation during hemodialysis. Conversely, low molecular weight heparins (LMWHs) have a more predictable metabolism and can be administered as a single bolus before dialysis, avoiding the need for a continuous infusion.[1,2] There now are numerous studies comparing these drugs with UH in hemodialysis patients that show similar efficacy, with no bleeding complications.[3-11] LMWHs also have a favorable effect on blood lipid levels compared with UH.[12-14] However, a paucity of data exists on the duration of action of LMWHs and, importantly, whether drug accumulation occurs with time given that these agents are renally excreted. The optimal dose in patients with renal failure also has not been determined.

Our experience with enoxaparin (Clexane; Aventis Pharma, Lane Cove, NSW, Australia) and dalteparin (Fragmin; Pharmacia Australia, Rydalmere, NSW, Australia), two commonly available LMWHs, is that significantly lower doses are needed to achieve adequate anticoagulation than those recommended by the manufacturer. We therefore were interested to assess the intensity and duration of the anticoagulant effect at these lower doses, but also to check for evidence of drug accumulation. Danaparoid sodium (Orgaran; Organon Australia, Lane Cove, NSW, Australia) also is an alternative to UH, but because it contains no heparin molecules, its use is primarily in patients with type II heparin-induced thrombocytopenia.[1,15] Like LMWHs, it is renally excreted, and again, data are limited on its use in chronic hemodialysis patients. We thus performed a prospective randomized study of enoxaparin and dalteparin at our routinely prescribed lower doses plus danaparoid sodium at its recommended dose in stable hemodialysis

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patients to assess their duration of action and examine for evidence of drug accumulation.

METHODS

Study Population and Protocol

Patients with end-stage renal disease undergoing chronic hemodialysis at the Sunshine Hospital satellite hemodialysis unit were recruited into the study. All patients underwent thrice-weekly 4-hour hemodialysis sessions. At this unit, all patients routinely undergo anticoagulation with an LMWH, either enoxaparin or dalteparin. Inclusion criteria were age older than 18 years and stable on chronic hemodialysis therapy for at least 3 months before recruitment. Exclusion criteria were current administration of oral anticoagulants; known hypersensitivity to enoxaparin, dalteparin, or danaparoid sodium; history of heparin-induced thrombocytopenia; dialysis through a central venous catheter; or vascular access thrombosis within 3 months of study start. The study protocol was approved by the Royal Melbourne Hospital Research Foundation Clinical Research and Ethics Committee.

After obtaining written informed consent, subjects were randomly assigned to one of three regimens: dalteparin, 2,500-U intravenous (IV) bolus; enoxaparin, 40-mg IV bolus; or danaparoid sodium, 35-U/kg IV bolus. Before starting their allocated treatment regimens, all patients initially underwent a 2-week (six-treatment) washout period in which UH was administered for anticoagulation. Chosen doses of both dalteparin and enoxaparin were those routinely administered in our unit. The dose of danaparoid sodium was based on results from two previous studies.[16,17]

Baseline predialysis blood tests were performed to determine hemoglobin level, activated partial thromboplastin time, prothrombin ratio (expressed as the international normalized ratio), and antifactor Xa activity just before beginning treatment with the allocated study drug. Anticoagulation was performed using the randomly assigned drug for 4 weeks (12 hemodialysis sessions). To assess the effectiveness and duration of anticoagulation, antifactor Xa levels were measured at the end of weeks 1 (the subject's hemodialysis treatment 3) and 4 (treatment 12), with blood drawn immediately before the injection and at 1, 2, 3, 4, 24, and 48 hours postinjection. Hemoglobin concentrations also were measured weeks 1 and 4. Pretreatment and posttreatment blood urea nitrogen levels were measured for calculation of urea reduction ratios at the end of weeks 1 and 4. Patients were started on the study so that the index treatment used for the measurement began during a midweek dialysis session, not after a long break. Both dialyzers and blood catheters were inspected for evidence of clotting at the end of each treatment and graded according to the following four-point scale: 1, no evidence of clotting; 2, fibrin formation in the dialyzer at the end of dialysis; 3, fibrin formation requiring additional anticoagulation during the treatment; and 4, completely clotted catheters requiring a replacement set. Time to hemostasis after needle removal was not formally assessed, but both the treating dialysis nurses and patients were required to note if they believed there had been a change in time to hemostasis as a result of a change in study treatment. Each patient also was monitored closely for evidence of bleeding postdialysis during the study period.

Twenty-one patients (seven subjects in each group) were enrolled into the study. During the 2-week washout period, three subjects withdrew from the study at their own request (two subjects, dalteparin group; one subject, enoxaparin group). All patients underwent dialysis through a native arteriovenous fistula or an arteriovenous graft as 4-hour thrice-weekly hemodialysis sessions. Blood flow rates were between 300 and 350 mL/min, and dialyzer flow rates for all patients were 500 mL/min. Causes of renal failure were as follows: glomerulonephritis, n = 8; reflux nephropathy, n = 3; diabetic nephropathy, n = 3; hypertension, n = 2; and unknown, n = 2. There were 10 women and 8 men on the study.

Seventeen subjects completed the study. One subject (dalteparin group) withdrew during week 3 of the study after being hospitalized for an arteriovenous graft infection. Data for this patient from week 1 are included in the analysis. In the dalteparin group, one patient missed the 24-hour blood test for antifactor Xa level week 1, and another patient, at 1 hour in week 4. In the enoxaparin group, two patients inadvertently had the 48-hour blood tests at week 1 performed after the injection of study drug, and another patient missed the 48-hour blood test at week 4. In the danaparoid sodium group, one patient missed both the 24- and 48-hour antifactor Xa blood levels at week 1, and another patient missed the 48-hour week-4 blood test.

Laboratory Methods

All blood tests were performed at the same central laboratory. Antifactor Xa activity was determined using chromogenic assay (Instrumentation Laboratory Co, Lexington, MA).

Statistical Analysis

All data are presented as mean ± SEM. Comparisons among the three treatments weeks 1 and 4 were performed using one-way analysis of variance, and for each drug between weeks 1 and 4, paired *t*-tests. All analyses were conducted using Graph Pad Prism, version 3.0 (Graphpad Software Inc, San Diego, CA). We declared a finding to be statistically significant for a two-sided *P* less than 0.05.

RESULTS

Duration and Intensity of Systemic Anticoagulation

The overall mean dosage for enoxaparin was 0.7 mg/kg, and for dalteparin, 39 U/kg. Tables 1 and 2 list the intensity of anticoagulation for each drug weeks 1 and 4, respectively. Profiles of the three drugs are shown in Figs 1 and 2. All three drugs provided adequate clinical systemic anticoagulation. There was no difference among the three drugs with respect to peak anticoagulant levels in the first hour of treatment.

There were significant differences among the three drugs with respect to duration of systemic anticoagulation at both weeks 1 and 4 (Tables 1

Table 1. Antifactor Xa Activity at the End of Week 1

	Antifactor Xa Activity (U/mL)			
Week 1	Enoxaparin	Dalteparin	Danaparoid	*P*
Baseline	0.05 ± 0.031	0.004 ± 0.004	0.12 ± 0.007*†	0.002
1 H	0.75 ± 0.046	0.58 ± 0.072	0.67 ± 0.051	0.15
2 H	0.61 ± 0.045	0.42 ± 0.054	0.65 ± 0.071	0.044
3 H	0.46 ± 0.022‡	0.29 ± 0.045	0.58 ± 0.05§	0.0012
4 H	0.38 ± 0.023‡	0.20 ± 0.035	0.54 ± 0.052*§	0.0002
24 H	0.08 ± 0.01‡	0.01 ± 0.008	0.22 ± 0.021§‖	<0.0001
48 H	0.04 ± 0.015	<0.01	0.13 ± 0.039¶	0.0263

*$P < 0.05$, danaparoid sodium versus enoxaparin.
†$P < 0.01$, danaparoid sodium versus dalteparin.
‡$P < 0.05$, Enoxaparin versus Dalteparin.
§$P < 0.001$, danaparoid sodium versus dalteparin.
‖$P < 0.001$, danaparoid sodium versus enoxaparin.
¶$P < 0.05$, danaparoid sodium versus dalteparin.

and 2). Danaparoid sodium produced a significantly longer duration of anticoagulation compared with both enoxaparin and dalteparin. Week 1, antifactor Xa activity for danaparoid sodium was significantly greater at 3, 4, and 24 hours versus dalteparin ($P < 0.001$) and at 4 and 24 hours versus enoxaparin ($P < 0.05$ and $P < 0.001$, respectively). At 48 hours, levels were still significantly greater for danaparoid sodium versus dalteparin ($P < 0.05$). At the end of week 4, results were similar, with antifactor Xa activity significantly greater for danaparoid sodium at 3, 4, and 24 hours versus dalteparin ($P < 0.01$, $P < 0.001$, and $P < 0.001$, respectively) and at 4 and 24 hours versus enoxaparin ($P < 0.01$ and $P < 0.001$, respectively). Subjects randomly assigned to enoxaparin therapy also had greater levels of anticoagulation compared with dalteparin 3, 4, and 24 hours postdose ($P < 0.05$) at the end of week 1, but this did not persist at the end of week 4.

Drug Accumulation

Pharmacokinetics of individual drugs were compared weeks 1 and 4. Antifactor Xa levels at all times were not significantly different week 4 versus week 1 for enoxaparin and dalteparin. For danaparoid sodium, levels 1 ($P = 0.0328$), 2 ($P = 0.0031$), 3 ($P = 0.0128$), and 4 hours ($P = 0.0121$) postdose were significantly greater week 4 compared with week 1, thus showing that the drug had not achieved steady state by the end of week 1 (Table 3). Importantly, patients allocated to danaparoid sodium therapy still

Table 2. Antifactor Xa Activity at the End of Week 4

	Antifactor Xa Activity (U/mL)			
Week 4	Enoxaparin	Dalteparin	Danaparoid	*P*
Baseline	0.03 ± 0.009	<0.01	0.07 ± 0.026	0.05
1 H	0.70 ± 0.053	0.70 ± 0.102	0.74 ± 0.059	0.84
2 H	0.57 ± 0.047	0.49 ± 0.064	0.72 ± 0.062	0.051
3 H	0.48 ± 0.042	0.34 ± 0.033	0.66 ± 0.062*	0.0035
4 H	0.4 ± 0.055	0.26 ± 0.038	0.65 ± 0.05†‡	0.0005
24 H	0.10 ± 0.018	<0.01	0.31 ± 0.039†§	<0.0001
48 H	0.05 ± 0.008	0.01 ± 0.009	0.08 ± 0.027	0.09

*$P < 0.01$, danaparoid sodium versus dalteparin.
†$P < 0.001$, danaparoid sodium versus dalteparin.
‡$P < 0.01$, danaparoid sodium versus enoxaparin.
§$P < 0.001$, danaparoid sodium versus enoxaparin.

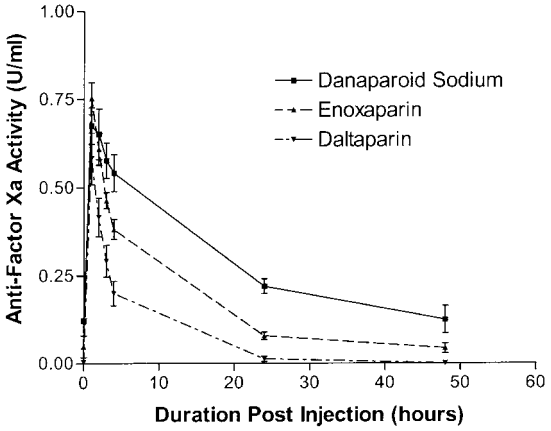

Fig 1. Antifactor Xa activity week 1 (mean ± SEM).

showed systemic anticoagulation 24 hours post-dose (Table 3).

Adverse Effects

All dialyzers received a grade of 1 for the assessment of fibrin/clot formation; thus, there were no episodes of catheter or dialyzer clotting during the study in any group. There was no significant difference among urea reduction ratios for each of the three drugs week 4 compared with week 1 (Table 4). In addition, there was no difference among hemoglobin concentrations for the three drug regimens at baseline, week 1, or week 4 (Table 4). Neither patients nor nursing staff reported prolongation of hemostasis after needle removal at the end of the dialysis session, and no adverse effects that could be attributable to the study drug were noted during the study. As

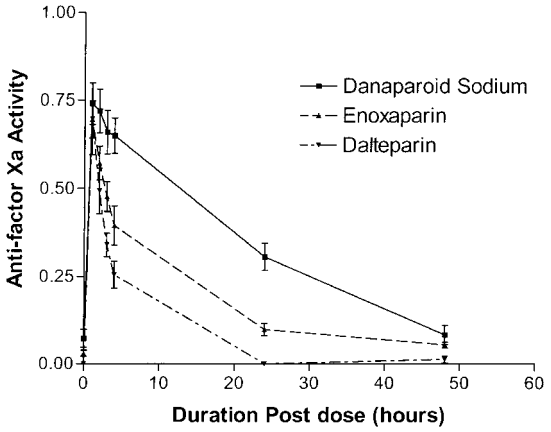

Fig 2. Antifactor Xa activity week 4 (mean ± SEM).

Table 3. Comparison Between Antifactor Xa Activity for Danaparoid Sodium at Weeks 1 and 4

Danaparoid Sodium	Antifactor Xa Activity (U/mL)		
	Week 1	Week 4	*P**
Baseline	0.12 ± 0.007	0.07 ± 0.026	0.14
1 H	0.67 ± 0.051	0.74 ± 0.059	0.0328
2 H	0.65 ± 0.071	0.72 ± 0.062	0.0031
3 H	0.58 ± 0.05	0.66 ± 0.062	0.0128
4 H	0.54 ± 0.052	0.65 ± 0.05	0.0121
24 H	0.22 ± 0.021	0.31 ± 0.039	0.0512
48 H	0.13 ± 0.039	0.08 ± 0.027	0.13

*Paired *t*-test.

noted, one patient was admitted to the hospital for an arteriovenous graft infection and subsequently withdrew from the study.

DISCUSSION

Despite being available for a number of years, to date, there are no established guidelines for dosages of the LMWHs dalteparin and enoxaparin in patients on chronic hemodialysis therapy. We show that routine anticoagulation can be performed effectively and safely with each of these agents at doses well less than those recommended by the manufacturers.

For dalteparin, we administered a single bolus of 2,500 U, which corresponded to a mean dose of 39 U/kg. Of the three drugs studied, it produced the lowest levels of systemic anticoagulation without evidence of blood lines or dialyzer clotting. There have been a number of studies published comparing dalteparin with UH that showed its efficacy in hemodialysis.[3,4,9,10,18,19] Some administered dalteparin as a bolus followed by a continuous infusion,[3,4,18] whereas others administered a single bolus dose only.[9,10,19] Substantial dose variations have been used in the latter group. Ljungberg et al[9] compared a single dose of 5,000 U of dalteparin with UH, with mean antifactor Xa activity at 4 hours of 0.76. Efficacy assessed by fibrin formation was similar to UH, and there were no significant adverse effects. A recent open prospective study assessed the effect of decreasing doses of dalteparin in 12 hemodialysis patients during 84 dialysis sessions.[10] The mean dose of dalteparin administered on the study was 2,665 IU (39 IU/kg), and the average elimination half-life was 2.2 hours

Table 4. Hemoglobin Levels and Urea Reduction Ratios for Each Drug Regimen

	Hemoglobin (g/L)			Urea Reduction Ratio (%)	
Drug	Baseline	Week 1	Week 4	Week 1	Week 4
Enoxaparin	10.8 ± 0.6	11.4 ± 0.5	11.7 ± 0.5†	68.3 ± 4.6	72.1 ± 1.0*
Dalteparin	12.1 ± 0.2	11.9 ± 0.4	12.1 ± 0.6†	71.2 ± 1.8	65.9 ± 1.7*
Danaparoid sodium	12.0 ± 0.4	12.1 ± 0.6	11.8 ± 0.3†	67.2 ± 2.1	66.6 ± 2.8*

*No significant difference between URR weeks 1 and 4.
†No significant difference between hemoglobin levels at each time.

during the dialysis session. This single dose of dalteparin effectively inhibited coagulation in the dialyzer and dialysis lines. Finally, Leu et al[19] studied the efficacy of even lower bolus doses in 33 hemodialysis patients with bleeding tendencies. In this study, patient dose was titrated from an initial bolus dose of 1,000 IU depending on the coagulation of blood lines. At the end of 6 months of treatment, mean dalteparin dosage was 1,152 ± 574 IU. Mean antifactor Xa levels were 0.34 ± 0.28 and 0.15 ± 0.09 IU/mL at 2 and 4 hours of dialysis, very similar to our study.

Using dalteparin, antifactor Xa activity at 4 hours postdose of 0.4 to 0.5 U/mL has been recommended as the target for patients on hemodialysis therapy.[2] Given the results of our study and those outlined previously, this target may be higher than necessary, and antifactor Xa levels of approximately 0.2 to 0.25 U/mL after 4 hours of dialysis probably are sufficient. The different methods used to determine antifactor Xa activity result in inherent difficulties comparing results from different studies; however, both the current findings and previous reports indicate that the majority of patients can undergo adequate anticoagulation with dalteparin after a single bolus dose of 2,500 U, suggesting that this should be the initial dose administered to patients for hemodialysis.

We found adequate anticoagulation with enoxaparin at a fixed dose of 40 mg. This corresponds to a dose of 0.7 mg/kg; again, less than that recommended by the manufacturer (1 mg/kg). Earlier studies showed satisfactory anticoagulation with enoxaparin at doses of 0.75 and 0.88 mg/kg,[20,21] and in one report, the starting dose of 1 mg/kg was reduced to 0.69 mg/kg because of minor bleeding disorders.[11] At this dose, no further bleeding difficulties were encountered, although unfortunately, antifactor Xa activity was not recorded. Antifactor Xa activity in the second half of the dialysis session on the current study was greater for enoxaparin compared with dalteparin, although this was only statistically significant in the first week. Given our results with dalteparin, anticoagulation using a lower dose of enoxaparin probably could be performed without loss of efficacy. In addition, we found no evidence for the accumulation of enoxaparin at 4 weeks.

Danaparoid sodium is an anticoagulant that consists of a mixture of heparan sulfate, dermatan sulfate, and chondroitin sulfate.[15] Importantly, it does not contain heparin or LMWH species and therefore has a role in the treatment of patients with type II heparin-induced thrombocytopenia.[15] Danaparoid sodium, like the LMWHs, is excreted by the kidneys; therefore, its action is prolonged in patients with renal failure. Its elimination half-life in hemodialysis patients is 30.8 hours compared with 18.4 hours in healthy volunteers.[16] We based our bolus dose on two previous dose-finding studies.[16,17] There was no difference in peak levels of anticoagulation among the three drugs. However, compared with both dalteparin and enoxaparin, danaparoid produced a significantly longer systemic anticoagulant effect. Patients administered danaparoid showed significantly anticoagulation 24 hours postdose, and antifactor Xa activity at the end of week 4 was significantly greater, indicating that the drug had not reached a steady state by the end of the first week. Only one study assessed the duration of anticoagulation for danaparoid sodium.[22] Comparisons are difficult given the different doses administered on the study; however, antifactor Xa activity was maintained during 6 hours postdose, and they also were able to detect residual antifactor Xa activity at 72 hours postinjection. Although we did not experience bleeding

complications, levels of systemic anticoagulation at 24 hours suggest that the danaparoid dose could be reduced safely without loss of efficacy. Further studies are required to establish the optimal danaparoid dose in hemodialysis patients. Given the increased antifactor Xa activity after 4 weeks of treatment, some caution is advised with prolonged use of the drug.

In conclusion, LMWHs represent an excellent alternative to UH for anticoagulation during hemodialysis. We show that these drugs can be administered safely at low doses without loss of efficacy. We did not find evidence of drug accumulation despite renal elimination of the drugs. Conversely, danaparoid sodium has a longer half-life, and at current recommended doses, does not reach steady-state levels within 4 weeks of treatment. Patients also showed significant anticoagulation 24 hours after injection, indicating that the current recommended dosage could be reduced.

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