

Preemptive dosage reduction of nadroparin in patients with renal failure: a retrospective case series

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Abstract

Background. Low-molecular-weight heparins (LMWHs) are frequently used to treat arterial and venous thrombo-embolic events. LMWHs accumulate with renal failure, but only limited clinical data regarding appropriate dosage adjustments are available. Nevertheless, LMWHs are routinely used in these patients worldwide. Although many clinics apply renal function-based dosage reductions, anti-factor Xa (anti-Xa) activity is not measured routinely.

Methods. We determined anti-Xa activity in 51 patients with MDRD-eGFR <60 mL/min/1.73 m², treated with therapeutic doses of nadroparin according to a standard, renal function-based guideline.

Results. An *a priori* dosage reduction resulted in anti-Xa activity within, below and above the reference range in 51, 30 and 19% of the measurements, respectively. Treatment resulted in different anti-Xa activities compared with dosages that were not given according to official advice ($P < 0.001$). Anti-Xa values increased with longer treatment duration ($P = 0.038$).

Conclusions. A preemptive fixed reduction (25%) of the nadroparin dosage in all patients with renal failure seems appropriate. However, because target anti-Xa activities were reached in only half of the patients, we submit that the use of nadroparin, dosage reduction and monitoring of anti-Xa activity in combination with clinical outcome monitoring in this patient population urgently needs further investigation.

Keywords: anti-factor Xa activity; nadroparin; renal failure

Introduction

Low-molecular-weight heparins (LMWHs) are frequently used in the initial treatment of deep venous thrombosis and pulmonary embolism. Their use is convenient compared with the continuous administration of unfractionated heparin, since they are administered once or twice daily by subcutaneous injections. Owing to their predictable anticoagulant effect, regular laboratory monitoring is not deemed necessary [1]. However, in special patient populations, in which uncertainties on the pharmacokinetic properties of LMWHs exist (e.g. decreased renal function, obesity and pregnancy), anti-factor Xa (anti-Xa) activity measurements may be used to monitor and optimize the anticoagulant effect of LMWHs [2, 3].

Limited clinical data on appropriate dosage adjustments for nadroparin based on anti-Xa activity in patients with renal failure are available [3]. This lack of knowledge on adequate nadroparin dosages in these populations increases both the risks of therapy failure and the occurrence of side effects.

Reduced renal clearance of LMWHs in patients with renal failure may lead to the accumulation of the LMWH and stronger anticoagulation effects as a result [4–6]. Indeed, for enoxaparin, a higher bleeding risk has been found for patients with renal failure who receive therapeutic treatment [7, 8]. Despite the fact that the use of LMWHs in patients with glomerular filtration rates (GFR) <30 mL/min is not recommended both in literature and by manufacturers [4, 9], in clinical practice, LMWHs are widely used in standard doses in the treatment of patients with varying levels of renal failure.

Therefore, we drafted and implemented a local clinical guideline including a mandatory dosage reduction of ~25% for patients with reduced renal function who were treated with therapeutic doses of nadroparin. To verify the appropriateness of this dosage reduction, we included routine anti-Xa activity measurements in these patients. After implementing the guideline, we collected all available clinical data from the medical records in order to assess adequacy of guideline implementation. Our main

objective was to calculate the percentage of anti-Xa activities that fell within the reference range for dosages that had been adjusted according to the guideline. As secondary objectives, we studied anti-Xa activity in relation to treatment duration. Here, we report these observational data.

Subjects and methods

This study represents a retrospective cohort study on anti-Xa activities in patients with renal failure and anticoagulation with nadroparin.

Setting and participants

A clinical guideline that dictated a preemptive dosage reduction of nadroparin for patients with renal failure was introduced in the internal medicine ward (Meander Medical Centre, Amersfoort, The Netherlands). The guideline applied to all patients with MDRD-eGFR <60 mL/min/1.73 m² in this ward, regardless of the origin of renal failure, who were hospitalized and received therapeutic doses of nadroparin. Patients were included from April 2010 to April 2012. Anti-Xa activities were ordered by the treating physicians during the patients' hospital stay. The numbers of bleeding and rethrombotic events were counted from the medical files retrospectively. The observation period was 1 month after the start of nadroparin treatment.

On request, the local institutional review board (IRB) of Meander Medical Centre confirmed that IRB exemption was approved for the collection and analysis of anti-Xa activities.

Dosage adjustments

The guideline comprised ~25% dosage reduction in nadroparin, based on the manufacturer's advice for patients with eGFR 30–50 mL/min. Prophylactic dosages were not adjusted nor monitored by anti-Xa activity measurement. The guideline is shown in Figure 1. A reduced starting dosage of 3800 IE nadroparin twice daily was advised for patients with a body weight <70 kg. In patients with a body weight >70 kg, a reduced starting dosage of 5700 IE nadroparin twice daily was advised.

Anti-Xa activity measurements

Anti-Xa activity measurements were preferably ordered on Day 4 and 8 of the treatment period, since we considered

that possible clinically relevant accumulation would occur after continued exposure. No sampling was performed on days of the weekend or public holidays. Blood samples were taken 4 h after subcutaneous administration of nadroparin to determine peak levels of anti-Xa activity. Adherence to the 4-h period between injection and sampling was warranted by the use of patient medication records on which the due times of administration are indicated. On all sampling requests, the laboratory was instructed to take samples 4 h after administration. Sampling times were verified from the laboratory report system.

Plasma samples were frozen immediately and at a later stage anti-Xa activity was measured using a one-step chromogenic assay according to the instructions of the manufacturer (Diagnostica Stago, Asnières-sur-Seine, France). The reference anti-Xa activity range 4 h after the administration of a therapeutic dose of nadroparin is 0.6–1.0 IE/mL [10]. Subsequent dosage adjustments were advised if anti-Xa levels fell outside this range; see Figure 1 for the algorithm. When treatment was continued for longer periods of time, additional anti-Xa measurements were performed; the second sample was ideally taken 4 days after the first anti-Xa measurement.

Statistics

Anti-Xa activities were plotted against corresponding renal functions. To explore the impact of nadroparin dosage on anti-Xa activity, all of the subjects were divided into three groups according to nadroparin dosage received [Group 1 received dosages according to the guideline, Group 2 received unadjusted dosages (higher than) the guideline, Group 3 received dosages lower than guideline]. The proportions of anti-Xa activity measurements that fell within or outside the reference range were calculated. Fisher's exact test for independence was used to test whether the proportion of anti-Xa activities within the reference range varied across guideline adherence, since six cells (67%) had an expected frequency of <5 (http://in-silico.net/tools/statistics/fisher_exact_test, consulted on 15 May 2013).

Each group was further subdivided into two subgroups: patients who had been on nadroparin treatment for a short period of time (Day 1–6) at the moment of sampling and patients who had been on nadroparin treatment for a longer period (Day 7 and further) at the moment of sampling. A two-way between-groups analysis of variance was conducted to explore the impact of nadroparin dosage and treatment duration on anti-Xa values.

We then divided all subjects that received dosages following the guideline and did not receive renal replacement therapy into four groups based on their renal function and duration of treatment (group 1: MDRD-eGFR <30 mL/min/1.73 m² treatment Day 1–6; group 2: MDRD-eGFR <30 mL/min/1.73 m² treatment Day 7 and further; group 3: MDRD-eGFR 30–60 mL/min/1.73 m² treatment Day 1–6; group 4: MDRD-eGFR 30–60 mL/min/1.73 m² treatment Day 7 and further) and plotted their mean anti-Xa activities against group number to explore the impact of the degree of renal function impairment and duration of treatment on anti-Xa activity. Data analysis was done in SPSS version 17.

Results

Patient characteristics are shown in Table 1. A total of 75 anti-Xa activity measurements were performed in

This guideline applies to all patients hospitalized on the Internal Medicine ward with MDRD-eGFR < 60 mL/min/1.73 m² who require therapeutic doses of nadroparin.

1. If weight < 70 kg: start dose = 3800 IE nadroparin bid
If weight > 70 kg: start dose = 5700 IE nadroparin bid
2. Order anti-Xa level measurement preferably at day 4 and 8
3. Reference levels (4 h after subcutaneous administration): 0.6–1.0 IE/mL
4. Adjust doses if necessary
 - If anti-Xa level < 0.6 IE/mL:
 - Raise 3800 IE nadroparin bid to 5700 IE nadroparin bid
 - Raise 5700 IE nadroparin bid to 7600 IE nadroparin bid
 - If anti-Xa level > 1.0 IE/mL:
 - Decrease 3800 IE nadroparin bid to 2850 IE nadroparin bid
 - Decrease 5700 IE nadroparin bid to 3800 IE nadroparin bid

Fig. 1. Guideline.

Table 1. Patient characteristics

	Total	Guideline adherence		
		Unadjusted (dosage above guideline)	Adjusted according to guideline	Overadjusted (dosage lower than guideline)
Number of anti-Xa measurements (in number of patients ^a)	66 (51)	10 (10)	47 (36)	9 (8)
Male/female (n)	25/26	3/7	18/18	4/4
Age (year), mean ± SD	73 ± 11	75 ± 12	74 ± 11	68 ± 9.8
Weight (kg), mean ± SD	78.5 ± 16.0 ^b	70.8 ± 14.7	78.5 ± 14.4 ^b	87.5 ± 21.4
Weight-adjusted dosage (IE/kg), mean ± SD	66 ± 18 ^c	93 ± 12 b.i.d.	65 ± 8 b.i.d. ^c	40 ± 10 b.i.d.
Renal function on Day 1 (n)				
MDRD-eGFR 30–60 mL/min/1.73 m ²	16	3	12	2
MDRD-eGFR 10–29 mL/min/1.73 m ²	15	4	12	2
MDRD-eGFR <15 mL/min/1.73 m ²	11	3	5	2
Renal replacement therapy	9	0	7	2

^aThe number of patients in the three right columns does not add up to 51, but to 54 since in one patient there were anti-factor Xa measurements corresponding to unadjusted, adjusted and overadjusted dosages and in one patient there were anti-factor Xa measurements corresponding to unadjusted and adjusted dosages. Therefore, these patients are counted in 2 and 1 extra column, respectively.

^bThe exact weight of two patients was not known (only the information that they weighed >70 kg). These patients are left out of the mean weight calculation.

^cThe exact weight of two patients was not known (only the information that they weighed >70 kg). These patients are left out of the mean weight adjusted dosage calculation.

57 patients from April 2010 to April 2012. In this time period, 5642 patients were hospitalized in the department of internal medicine. Of these 75 anti-Xa activity measurements, 9 measurements in 8 patients were excluded from analysis with the following reasons: MDRD-eGFR >60 mL/min/1.73 m² (n = 1), change to prophylactic therapy on the day of measurement (n = 1), sampling error (n = 4), nadroparin administration unsure (n = 1), sampling after cessation of nadroparin treatment (n = 2). First samples were taken between Day 3 and 14 after start of treatment.

In day-to-day clinical practice, not all the patients received nadroparin dosages according to the guideline. Some received unadjusted dosages (e.g. due to initial unfamiliarity with the guideline of the treating physician) and some received even lower than advised dosages (e.g. due to caution of the treating physician in high-risk patients) (Table 1). Dosage regimens and anti-Xa activities with corresponding MDRD-eGFR on the first day of nadroparin treatment are shown in Figure 2.

With an *a priori* dosage reduction, anti-Xa activity was adequate in 51% of the measurements. However, in 30% of the measurements, anti-Xa activity fell below the reference range and in 19% anti-Xa activity was higher than the reference range. Unadjusted (higher than the guideline) dosages led to anti-Xa levels higher than reference values in 60% of the cases. If nadroparin dosages were reduced even more than advised in the guideline, 67% of the anti-Xa measurements fell below the reference range. Fisher's exact test for independence indicated a significant association between guideline dosage adherence and anti-Xa activity within the reference range (P = 0.009).

Division of each of these three dosage adherence groups into two subgroups of patients who were treated for a shorter time period (up to Day 6) and longer time period (Day 7 and further) resulted in six subgroups (Figure 3). Group 1: dosage below the guideline, treatment Day 1–6 (n = 4); Group 2: dosage according to the guideline, treatment Day 1–6 (n = 29); Group 3: dosage above the guideline, treatment Day 1–6 (n = 7); Group 4: dosage below the guideline, treatment Day 7 and further (n = 5); Group 5: dosage according to the guideline, treatment Day 7 and further (n = 18); Group 6: dosage above the

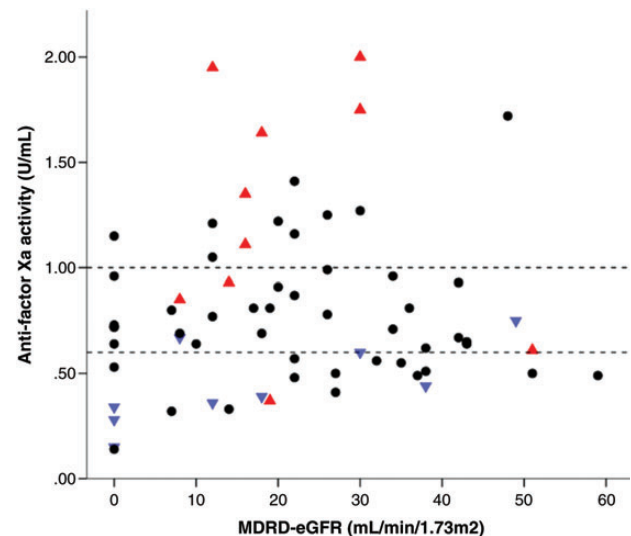


Fig. 2. Anti-factor Xa activity measurements at differing levels of renal function. Renal function was determined on the first day of nadroparin usage. Each symbol represents an anti-Xa activity measurement. Blue triangles represent patients who received nadroparin dosages lower than the guideline (n = 9). Black dots represent patients who received nadroparin dosages adjusted according to the guideline (n = 47). Red triangles represent patients who received unadjusted nadroparin dosages above the guideline (n = 10). For clarity reasons, renal function of all participating renal replacement therapy patients was set at MDRD-eGFR 0 mL/min/1.73 m². Dashed lines represent the upper and lower limit of the reference range.

guideline, treatment Day 7 and further (n = 3). Mean anti-Xa activities were 0.31, 0.75, 1.13, 0.55, 0.81 and 1.56 U/mL, respectively. The mean anti-Xa activity of dosages below the guideline fell below the reference range; mean anti-Xa activity of unadjusted dosages (higher than the guideline) tended to fall above the reference range. The mean anti-Xa activity of dosages according to the guideline fell within the reference range. There was a statistically significant main effect for protocol adherence (P < 0.001) and for the duration of treatment (P = 0.038).

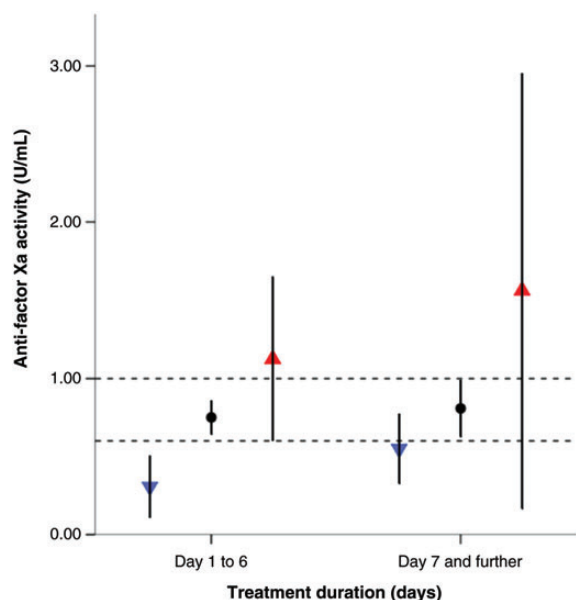


Fig. 3. Mean anti-Xa activity per dosage group and treatment duration. Vertical lines at the measuring points indicate the 95% confidence intervals. Blue triangles represent patients who received nadroparin dosages lower than the guideline ($n=4$ for Day 1–6, $n=5$ for Day 7 and further). Black dots represent patients who received nadroparin dosages adjusted according to the guideline ($n=29$ for Day 1–6, $n=18$ for Day 7 and further). Red triangles represent patients who received unadjusted nadroparin dosages above the guideline ($n=7$ for Day 1–6, $n=3$ for Day 7 and further). Dashed lines indicate the upper and lower limit of the reference range.

The interaction effect between protocol adherence and treatment duration was not statistically significant.

To explore a possible influence of the extent of renal function impairment on anti-Xa activity, we divided the patients who received nadroparin dosages as per the guideline and who were not on renal replacement therapy into four groups based on the degree of renal function impairment on the first day of treatment and duration of treatment on the moment of sampling. Group 1: MDRD-eGFR <30 mL/min/1.73 m² Day 1–6 ($n=15$); Group 2: MDRD-eGFR <30 mL/min/1.73 m² Day 7 and further ($n=8$); Group 3: MDRD-eGFR 30–60 mL/min/1.73 m² Day 1–6 ($n=9$) and Group 4: MDRD-eGFR 30–60 mL/min/1.73 m² day further ($n=7$) (Figure 4). Mean anti-Xa activities were 0.74, 0.95, 0.79 and 0.72 U/mL, respectively. Group sizes were too small to justify statistical analysis; however, from Figure 4, it can be hypothesized that at least for patients with MDRD-eGFR <30 mL/min/1.73 m² accumulation of nadroparin should be taken into account since anti-Xa activity seems to increase with time.

The guideline advises additional dosage adjustments when anti-Xa activities fall outside the reference range. In 15 patients, dosage adjustments were made. However, in only two of these patients was a follow-up measurement of anti-Xa activity performed. This is mainly because treatment was ceased or patients were discharged from the hospital before additional anti-Xa measurements were ordered for the other patients.

There were 12 patients in whom a second anti-Xa measurement was done while on the same dosage (Supplementary data).

Seven patients experienced a bleeding event, five cases of which an influence of nadroparin could not be excluded. In two patients, re-thrombotic events were

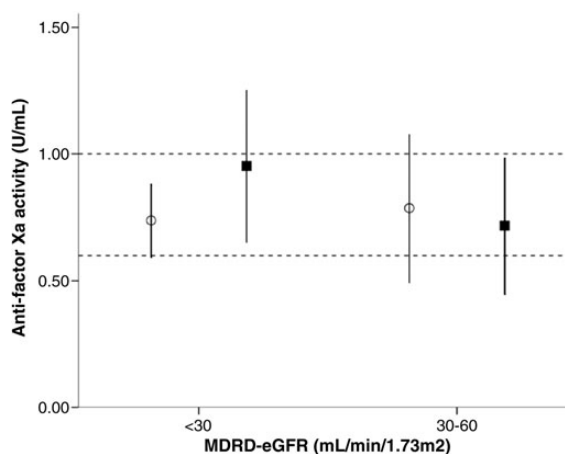


Fig. 4. Mean anti-Xa activity per degree of renal impairment and treatment duration. All of the patients received nadroparin dosages according to the protocol. Vertical lines at the measuring points indicate the 95% confidence intervals. Open circles represent patients who received nadroparin for 1–6 days at the time of measurement ($n=15$ for <30 mL/min/1.73 m², $n=9$ for 30–60 mL/min/1.73 m²). Black squares represent patients who received nadroparin for 7 days or longer at the time of measurement ($n=8$ for <30 mL/min/1.73 m², $n=7$ for 30–60 mL/min/1.73 m²). Dashed lines represent the upper and lower limit of the reference range.

described. Details are available in Supplementary data. Numbers are too small to evaluate the association between anti-Xa activity and the occurrence of bleeding or re-thrombotic events.

Discussion

This is one of the first clinical audits to report attained anti-Xa activity levels in patients with reduced renal function treated with therapeutic doses of nadroparin using an *a priori* dosage reduction. Our main finding is that an *a priori* ~25% nadroparin dosage reduction in patients with impaired renal function resulted in adequate anti-Xa activity in 51% of the cases.

Mean anti-Xa activities varied significantly between the three dosage groups (guideline adherence versus unadjusted or overadjusted dosages). Unadjusted dosages led to mean anti-Xa values above the reference range and overadjusted dosages led to mean anti-Xa values below the reference range.

We found a small effect of duration of treatment on mean anti-Xa increase. As there were several measurements per person for some persons (Table 1), a longitudinal analysis procedure would have been better. However, this pilot study did not have enough data points for this procedure. Although not statistically tested due to small group sizes, this accumulation of the effect of nadroparin on anti-Xa activity with time seems most distinct in patients with MDRD-eGFR <30 mL/min/1.73 m² compared with MDRD-eGFR 30–60 mL/min/1.73 m². This seems plausible, since renal clearance of nadroparin would most likely be affected in patients with the worst renal function.

However, there are major concerns when applying these findings to all of the patients with eGFR <60 mL/min. Firstly, 49% of the anti-Xa activity measurements still fell outside the reference range, both above the upper limit and below the lower limit, which may increase the risks of side effects and therapy failure, respectively. Measuring anti-Xa levels currently is the generally accepted method to verify

adequate LMWH dosing [1, 6], but it should be noted that its use has not been validated [11].

Secondly, the objective of the analysis was to evaluate the impact of the clinical guideline on attained anti-Xa levels, and the analysis was not designed to correlate the resulting anti-Xa activities to clinical outcomes. Thus, we did not prospectively document clinical outcomes such as number of bleeding and re-thrombotic events nor was the analysis powered to do so.

Considering both the lack of data on adequate LMWH dosage adjustments in renal failure and our results which seem to justify an *a priori* dosage adjustment, we would like to emphasize the importance of further research. Renal patients constitute a large population for which questions remain regarding LMWH treatment. Differences between LMWHs should be considered. These nadroparin results cannot be extrapolated to other LMWHs, since the LMWHs differ in pharmacokinetic and pharmacodynamic profiles. Theoretically, nadroparin might even not be the LMWH of choice in patients with reduced renal function, because its relatively small molecular weight renders its elimination mainly dependent on renal function. Tinzaparin, for example, has a higher molecular weight and is less dependent on renal function for its elimination. Therefore, tinzaparin might have a lower risk of accumulation in kidney patients than the smaller LMWHs [4].

Although most dependent on renal clearance, most evidence of all LMWHs on altered pharmacokinetics exists for the use of enoxaparin [1] including dose-adjusting schemes [4, 12–14]. Nevertheless, in a national questionnaire among Dutch nephrologists, it was found that in 56% of the Dutch hospitals nadroparin was the LMWH of choice to treat embolic diseases (data not shown).

Based on pharmacokinetic modelling of enoxaparin, two studies report that with a loading dose followed by a lower maintenance dose adequate anti-Xa activities are reached in a timely manner without subsequent accumulation [12, 13].

An important limitation of this study is that it is a retrospective analysis and not a clinical randomized trial. A prospective randomized trial in patients with renal failure would be needed, powered for clinical endpoints to answer appropriately the question whether a pre-emptive dosage reduction along with anti-Xa activity measurements is adequate.

In conclusion, an *a priori* dosage reduction in nadroparin of ~25% in all of the patients with reduced renal function resulted in adequate anti-Xa levels more often than when no dose reduction was applied. However, to draw definitive conclusions on dosing advice for therapeutic use of nadroparin and other LMWH in patients with renal failure, prospective studies that include clinical outcomes are urgently needed, exploring optimal dosage reductions and the role of anti-Xa activity in dose titration.

Supplementary data

Supplementary data is available online at <http://ndt.oxfordjournals.org>.

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Conflict of interest statement. None declared.

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