Is Impaired Renal Function a Contraindication to the Use of Low-Molecular-Weight Heparin?

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Background: Because of the risk of accumulation of anticoagulant effect, it has been suggested that patients with a creatinine clearance of 30 mL/min or less (<0.50 mL/s) should be excluded from treatment with low-molecular-weight (LMW) heparin, or have anti–factor Xa heparin level monitoring performed.

Objective: To assess the appropriateness of this recommendation.

Methods: We performed a systematic search of MEDLINE, EMBASE, and International Pharmaceutical Abstracts to identify prospective articles comparing differences in the pharmacokinetics of LMW heparins in nondialyzed patients with varying degrees of renal function. Reference lists of retrieved reports were checked for additional articles.

Results: Three single-dose pharmacokinetic trials and 2 multiple-dose deep vein thrombosis (treatment trials met our selection criteria. The 3 trials that could address our primary objective did not support the use of a 30-mL/min (0.50-mL/s) cutoff of creatinine clearance to select individuals at risk of accumulation when LMW heparin is used. Four of the 5 trials support the notion that anti–factor Xa activity of some LMW heparin preparations accumulates in patients with impaired creatinine clearance. Tinzaparin sodium, an LMW heparin with a higher-than-average molecular weight distribution, appears to be the exception, since it did not exhibit accumulation in patients with creatinine clearances as low as 20 mL/min (0.33 mL/s).

Conclusions: The use of a 30-mL/min (0.50-mL/s) cutoff is not justified, on the basis of currently available evidence, to select individuals at increased risk of accumulation when LMW heparin is used. The pharmacokinetic response to impaired renal function may differ among LMW heparin preparations.

Arch Intern Med. 2002;162:2605-2609

IN CONTRAST to the dose-dependent clearance of unfractionated heparin, the clearance of low-molecular-weight heparin is considered to be primarily via renal excretion.1 Consistent with reports in the literature,2,3 we have encountered a number of cases of severe hemorrhagic complications associated with the use of LMW heparin in patients with renal impairment. We therefore attempted to develop operational guidelines for the use of LMW heparin in patients with renal insufficiency.

An informal review of the literature identified 2 approaches to the treatment of patients with renal impairment who require parenteral anticoagulation. The first approach is to use anti–factor Xa heparin (anti-Xa) activity to monitor patients with renal insufficiency who are treated with LMW heparin.1,4 Problems with this method include (1) that the therapeutic range for anti-Xa heparin levels has not been validated and (2) that access to timely anti-Xa heparin activity assays is limited in many centers. The second approach is to replace unmonitored LMW heparin therapy with monitored unfractionated heparin therapy in patients with a creatinine clearance (CrCl) of less than 30 mL/min (<0.50 mL/s).5,7 The use of a calculated CrCl as a method for screening for patients at high risk of over-anticoagulation is attractive because of its ease of performance. However, it is not clear whether any particular cutoff in CrCl is a threshold below which there is a danger of accumulation of the anticoagulant effect of LMW heparin. Furthermore, there is evidence that suggests that the different LMW heparin preparations currently available may have very different risks of bioaccumulation in patients with impaired renal function.

We performed a systematic review of LMW heparin usage in patients with renal insufficiency with the goal of determining whether the commonly recommended 30 mL/min (0.50 mL/s) of CrCl is an appropriate cutoff to select patients for exclu-
sion from treatment with LMW heparin, or for anti-Xa monitoring, if LMW heparin is used.

**METHODS**

**SEARCH STRATEGY**

A systematic search was performed to locate articles comparing differences in the pharmacokinetics of LMW heparins in patients with varying degrees of renal function. MEDLINE (OVID, from 1966 to the week of March 3, 2001), EMBASE (OVID from 1980 to 2001 week 19), and International Pharmaceutical Abstracts (Silver Platter, from 1970 to April 2001) were searched without language restrictions by means of the free text and Medical Subject Headings terms ardeparin, Normiflo®, dalteparin, Fragmin®, habi 2165, enoxaparin, Lovenox®, Clexane®, PK-10169, nadroparin, Fraxiparin®, Fraxiparine®, Cy 216, parnaparin, reviparin, Clivarin®, tinzaparin, Innhocep®, logiparin, tedelparin, heparin, low-molecular-weight, kidney failure, renal failure, creatinine, renal function, and glomerular filtration rate. Reference lists of retrieved reports and review articles were checked for additional articles. The names of all authors of relevant articles were then used to search the cited reference field of the Science Citation Index (Institute for Scientific Information, from 1993 to May 17, 2001).

**SELECTION**

Only prospective trials that investigated the administration of a LMW heparin to nondialyzed patients with renal impairment were selected. An explicit cutoff of CrCl signifying renal impairment was not chosen. We excluded data derived from patients undergoing hemodialysis because CrCl could not be calculated for such patients. Data from review articles and animal studies were not considered.

**METHODOLOGIC QUALITY**

Potential sources of bias were identified and used as a means to explain discrepancies in results between the retrieved studies.

**DATA EXTRACTION**

The reports were screened and retrieved by one of us (J.N.). Prehex endpoints of interest were pharmacokinetic measures that indicate accumulation of anti-Xa activity. For single-dose studies, the measures of interest were elimination half-life ($t_{1/2}$) and area under the concentration time curves (AUCs). For multiple-dose studies, the maximum and minimum concentrations ($C_{max}$ and $C_{min}$) and the AUC were extracted.

The correlation coefficient for the relationship of calculated CrCl and clearance of anti-Xa activity was extracted from both single- and multiple-dose studies.

**RESULTS**

**TRIAL CHARACTERISTICS**

The search identified 304 citations that were screened for eligibility, most of which were excluded on the basis of the publication type (letter, review, or editorial) or study population (animal studies or patients receiving hemodi- 

alysis or hemofiltration). Of the 304 citations, only 9 met our inclusion criteria. Four of the 9 studies were subsequently excluded for the following reasons. One article published in French® contained data from the same 27 patients who were previously described in English®; thus, only data from the English trial were considered. One abstract contained data that were subsequently published in full. Finally, 2 studies published in abstract form only did not provide enough data for evaluation.

Three single-dose pharmacokinetic trials and 2 multiple-dose deep vein thrombosis treatment trials were eligible for inclusion. Table 1 highlights the applicable findings of the single-dose studies, and Table 2 outlines the results of the multiple-dose studies.

All studies included for review used chromogenic anti-Xa assays for determining plasma LMW heparin levels, which is the recommended method of the College
of American Pathologists, Most one study used the S 2222 KB VITRUM kit (Kabi Vitrum, Stockholm, Sweden),14 while 4 studies used the Stachrom-heparin kit (Diagnostica Stago, Asnières, France).9,11,13,16

**SINGLE-DOSE STUDIES**

Hory et al14 compared the pharmacokinetics of a single intravenous dose of Cy 222 (250 U anti-Xa/kg) in 24 non-hemodialyzed patients with chronic renal failure with those of 10 healthy volunteers.14 The patients were grouped according to their CrCl into stage 1 (n=9, 30-50 mL/min [0.50-0.84 mL/s]), stage 2 (n=8, 10-30 mL/min [0.17-0.50 mL/min]), and stage 3 (n=7, <10 mL/min [<0.17 mL/s]). The authors did not specify the method used to determine CrCl.

Patients in stage 1 were on average 13.2 years younger and 19.8 kg heavier than stage 3 patients. All 9 patients in stage 1 were male, while 3 of 7 stage 3 patients were female. A significantly lower mean hemoglobin level was found in stage 3 patients than in stage 1 or 2 patients (9.6 vs 12.1 and 12.7 g/dL, respectively). Baseline characteristics were not provided for the control group.

The AUC was similar for all 4 groups. Patients in stage 3 had a significantly prolonged t\( \text{1/2} \) compared with all other groups. The authors stated that CrCl was significantly correlated with anti-Xa t\( \text{1/2} \) (P<0.002); however, no correlation coefficient was provided to indicate the strength of correlation. The results suggest that the clearance of Cy 222’s anti-Xa heparin activity is significantly altered in patients with severely impaired renal function (CrCl <10 mL/min [0.17 mL/s]) compared with patients with less severe or no renal impairment. The findings suggest that a cutoff of less than 10 mL/min in CrCl would identify patients at risk of significant accumulation of anti-Xa heparin activity.

Cadroy et al15 compared the kinetics of a single subcutaneous dose of enoxaparin sodium (50 IU/kg) in 12 healthy volunteers and 12 patients with chronic renal insufficiency (CRI) who had not yet undergone hemodialysis.15 The CrCls were calculated by the Siersbæk-Nielsen nomogram and ranged from 5 to 21 mL/min (0.08-0.35 mL/s) (mean, 11.4 mL/min [0.19 mL/s]) for the patients with CRI and 88 to 140 mL/min (1.47-2.34 mL/s) (mean, 105 mL/min [1.75 mL/s]) for the healthy subjects.

The patients with CRI were composed of 8 women and 4 men with a mean age of 58 years, and the healthy volunteers were 5 women and 7 men with a mean age of 23 years. The mean weight of the individuals of each group was not reported.

The mean t\( \text{1/2} \) in the impaired renal function group was significantly prolonged and the AUC significantly increased compared with the control group. It should be noted that the clearance of enoxaparin’s anti-Xa heparin effect in the control group was nearly twice that of volunteers in other kinetic studies of this LMW heparin, which may partly explain the apparent accumulation of anti-Xa heparin activity in the CRI group. There was no relationship between the severity of renal failure as measured by the CrCl and the total clearance of enoxaparin (r=−0.29, P>0.5); however, the lack of correlation may be partly explained by the narrow distribution of CrCls in the CRI group. This study indicates that anti-Xa heparin activity is prolonged in patients with CrCls between 5 and 21 mL/min (0.08 and 0.35 mL/s) after subcutaneous administration of enoxaparin. It is not possible to determine a cutoff point at which the risk of anti-Xa heparin activity accumulation increases from this study because of the narrow range of CrCls studied.

Goudable et al11 investigated the pharmacokinetics of nadroparin calcium after a single bolus intravenous injection (41.3 IU/kg) in 3 groups of patients affected by CRI of varying severity.11 Group A (n=7) was composed of patients receiving hemodialysis with a CrCl of less than 10 mL/min, patients in group B (n=7) had a CrCl ranging from 10 to 20 mL/min (0.17-0.33 mL/s), and patients in group C (n=5) had a CrCl of 30 to 50 mL/min (0.50-0.84 mL/s). A group of 12 healthy volunteers (CrCl, 75-200 mL/min [1.25-3.34 mL/s]) was investigated but not deemed a control group by the investigators because the ages were not matched. The method used to calculate CrCls was not provided.

The t\( \text{1/2} \) and AUC were similar in all 3 CRI groups. A significant difference was detected when these variables

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**Table 2. Characteristics and Results of the Multiple-Dose Studies Included for Review**

| Source | LMWH | Dose and Route | No. of Patients in Each Group | Mean CrCl, mL/min† | Mean ± SD AUC, aXa U/mL - h | Mean ± SD Cmax, IU/mL | Correlation Between CrCl and aXa
|--------|------|---------------|-------------------------------|------------------|----------------------|---------------------|-----------------
| Misretti et al.16 1998 | Nadroparin calcium | subcutaneously | 12 | 114 ± 15 | 15.3 ± 5.5 | 1.34 ± 0.40 | r = 0.49‡ |
| Siguret et al.9 2000 | Tinzaparin sodium | subcutaneously | 7 | >50 | Not reported | 0.65 ± 0.14 | No |

*LMWH indicates low-molecular-weight heparin; CrCl, creatinine clearance; aXa, anti-factor Xa; AUC, area under the concentration time curve; Cmax, maximum concentration; and IU, international aXa units. Day 1 and day n refer to the first and last days of administration, respectively.*

†To convert to milliliters per second, multiply by 0.0167.

‡P<0.001 vs healthy young volunteers.

§P<0.001 vs healthy elderly volunteers.

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were compared with those of the healthy subjects, indicating a faster elimination in the younger, healthy volunteers. No significant correlation existed between CrCl and the clearance of nadroparin in the patients with CRI, despite a larger spread of renal function (<10-50 mL/min [<0.17-0.84 mL/s]). The results support the notion that the $t_\text{1/2}$ of nadroparin’s anti-Xa heparin activity is prolonged in patients with calculated CrCl’s of less than 50 mL/min (<0.84 mL/s).

**MULTIPLE-DOSE TRIALS**

Mismetti et al. reported on the differences in pharmacokinetics between 3 groups of 12 individuals treated with a daily subcutaneous injection of nadroparin calcium (180 IU/kg) for 6 to 10 days. The first 2 groups were composed of healthy volunteers differing by age (25±4 and 65±3 years) and CrCl (114±15 and 62±6 mL/min [1.90±0.25 and 1.04±0.10 mL/s]). The third group was composed of hospitalized patients undergoing treatment for acute deep vein thrombosis (mean age, 65±11 years; CrCl, 76±8 mL/min [1.27±0.13 mL/s]). The authors did not state how CrCl’s were determined.

The $C_{\text{max}}$, $C_{\text{min}}$, and AUC after the last administration of nadroparin were significantly higher in both the deep vein thrombosis group and healthy elderly patients compared with the healthy young group, suggestive of an accumulation of drug.

A correlation coefficient was calculated for 2 comparisons. When all groups were considered, the correlation between the CrCl and the clearance of anti-Xa activity was 0.49 ($P<.002$). When the group of patients with deep vein thrombosis was excluded from the calculation, the correlation coefficient increased to 0.69 ($P<.001$). This study supports the relationship between renal function and the clearance of nadroparin’s anti-Xa heparin effect. However, it does not allow us to address the appropriateness of using a cutoff of 30 mL/min (0.50 mL/s), because insufficient numbers of patients were studied and few patients had very low CrCl’s.

Siguret et al. examined the pharmacokinetics of tinzaparin sodium (175 IU/kg) administered subcutaneously once daily for 10 days in 30 patients (6 male, 24 female) being treated for acute thromboembolic disease. Serum creatinine was measured on day 0, and CrCl’s were calculated by the Cockcroft formula. For analysis, the patients were grouped according to their CrCl into ranges of 50 mL/min and greater ($\geq 0.84$ mL/s) (n=7), between 40 and 49 mL/min (0.67 and 0.83 mL/s) (n=6), between 30 and 39 mL/min (0.50 and 0.66 mL/s) (n=9), and between 20 and 29 mL/min (0.33 and 49 mL/s) (n=8). The breakdown of age, weight, and sex for each group was not provided.

No increase in mean $C_{\text{max}}$ values was observed in any group after 10 days of administration of tinzaparin. The $C_{\text{max}}$ values during the 10 days were similar even when the group with CrCl’s greater than 50 mL/min (>0.84 mL/s) was compared with the group with CrCl’s between 20 and 30 mL/min (0.33 and 0.50 mL/s). The $C_{\text{min}}$ and AUC values were not provided. The clearance of anti-Xa activity and the CrCl were not correlated. The results of this study, completed in a group of patients with a wide distribution of CrCl’s (20 to >50 mL/min [0.33-0.84 mL/s]), indicate that the anti-Xa heparin effect of tinzaparin does not appear to accumulate as CrCl declines.

**COMMENT**

LMW heparin preparations are becoming the anticoagulant of choice for the treatment of venous thromboembolism and acute coronary syndromes, as they possess a number of advantages over unfractionated heparin. Unfortunately, LMW heparins also have the disadvantage that they can accumulate in patients with renal failure and therefore have the potential to produce serious bleeding in such patients. Accordingly, it would be desirable to develop guidelines for the management of LMW heparin in patients with renal failure.

The primary objective of our study was to perform a comprehensive review of the literature to determine whether the use of the recommended cutoff of 30 mL/min (0.50 mL/s) in CrCl is appropriate to select patients for exclusion from treatment with LMW heparins, or for anti-Xa heparin activity monitoring if an LMW heparin is used. Three studies included for review investigated patients with a large enough spread in CrCl to evaluate our primary objective. There were no data from these 3 trials to support the use of the currently recommended cutoff level of 30 mL/min. In keeping with current views, however, the results of 4 of the 5 trials reviewed support the notion that patients who have a reduction in calculated CrCl are at risk of accumulation of anti-Xa heparin activity when they are treated with certain LMW heparins. The exception appears to be the LMW heparin tinzaparin, which, in a small study, did not accumulate in patients with calculated CrCl’s as low as 20 mL/min (0.33 mL/s).

The 3 trials that allowed evaluation of the 30-mL/min (0.50-mL/s) cutoff provided conflicting findings. Hory et al. investigated the kinetics of a single dose of intravenously administered Cy 222 to patients grouped according to their CrCl, which ranged from less than 10 mL/min to greater than 50 mL/min. They determined that, despite similar AUC’s, patients with the most severely impaired renal function (CrCl <10 mL/min [<0.17 mL/s]) had a significantly prolonged $t_{\text{1/2}}$ of anti-Xa activity when compared with all other groups. Their findings therefore suggest that a cutoff of less than 10 mL/min in CrCl would identify patients at risk of significant accumulation of Cy 222. The results of this trial may not be applicable to other LMW heparin preparations, because Cy 222 has a mean molecular weight of 2500 d, nearly 50% smaller than the LMW heparins in clinical use today. The smaller size of Cy 222 likely causes a greater reliance on renal clearance than for the other LMW heparins included in this review.

In the second study, a single dose of intravenous nadroparin was administered to 3 groups of patients with CRI of varying severity (CrCl, <10 to 50 mL/min [<0.17 to 0.84 mL/s]). The $t_{\text{1/2}}$ and AUC were similar in all 3 CRI groups but were significantly larger than the same kinetic variables obtained from a group of healthy subjects, indicating a faster elimination in the healthy volunteers. The results of this study suggest that the anti-Xa activity of nadroparin may accumulate in patients with CrCl’s as high
Notably, no accumulation of anti-Xa heparin activity was evident in this study, even in the group of patients with CrCls less than 30 mL/min. Two factors may partly explain the contradictory results of the trial with tinzaparin. First, age-related reductions in glomerular filtration rate may not lead to the same degree of accumulation of anti-Xa activity as acute glomerular diseases. Second, tinzaparin has a higher molecular weight than other LMW heparin preparations and so would be expected to be less dependent on renal clearance (Table 3). This observation with tinzaparin raises the possibility that this LMW heparin might be the favored preparation in patients with impaired renal function. However, additional studies with tinzaparin, preferably comparing it with other LMW heparin preparations, would have to be performed before any evidence-based recommendations could be made.

In summary, there appears to be no justification for the use of a 30 mL/min (0.50 mL/s) cutoff in CrCl to select patients at increased risk of accumulation if LMW heparin is used. Using this cutoff for some LMW heparin preparations might be dangerous (as there is evidence that accumulation might occur in patients with higher CrCl) or might be overly cautious (as there is evidence that one LMW heparin does not accumulate even in patients with CrCl less than 30 mL/min). On the basis of the results of this review, it is not possible to make any conclusive recommendations for the management of LMW heparin therapy in patients with renal insufficiency. Data from trials using nadroparin, enoxaparin, and Cy 222 confirm the view that accumulation of anti-Xa heparin activity is possible in patients with renal impairment. In contrast, accumulation was not observed in a trial with the higher-molecular-weight agent tinzaparin. Therefore, a class effect for LMW heparin use in renal insufficiency should not be accepted because of (1) differences in the level of CrCl at which the risk of accumulation increases and (2) the failure to demonstrate accumulation with one preparation. Furthermore, there is evidence of variability in the pharmacokinetics of these products in patients with similar degrees of renal impairment as measured by the CrCl. This suggests that the type of renal injury should be considered in future investigations. Because of the scarcity of literature in this area, the potentially serious consequences of accumulation, and the increasing use of LMW heparin preparations, kinetic studies for each LMW heparin in patients with varying degrees of renal insufficiency are urgently required.

Accepted for publication April 3, 2002.

We thank Pamela Nagge for her editorial assistance.

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**Table 3. Anticoagulant Profiles and Molecular Weights for the Low-Molecular-Weight Heparins Investigated in Studies Included for Review**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Anti–Factor Xa to Anti–Factor IIa Ratio</th>
<th>Molecular Weight, d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enoxaparin sodium</td>
<td>4.1</td>
<td>4371</td>
</tr>
<tr>
<td>Nadroparin calcium</td>
<td>3.2:1</td>
<td>4555*</td>
</tr>
<tr>
<td>Tinzaparin sodium</td>
<td>1.9:1</td>
<td>5666*</td>
</tr>
<tr>
<td>Cy 222</td>
<td>10:1</td>
<td>2500</td>
</tr>
</tbody>
</table>

*Determined by gel permeation chromatography.*

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