Changes in the pharmacokinetics of the low-molecular-weight heparin enoxaparin sodium during pregnancy

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OBJECTIVE: We sought to evaluate the pharmacokinetics of subcutaneously administered enoxaparin sodium during and after pregnancy.

STUDY DESIGN: Daily subcutaneous injections of enoxaparin sodium (40 mg) were administered to 13 pregnant women. On 3 separate occasions, once early in pregnancy (12-15 weeks), once late in pregnancy (30-33 weeks), and once in the nonpregnant state (6-8 weeks post partum), serial blood samples were collected, and plasma was analyzed for antifactor Xa activity. Analysis of variance was used for statistical analysis. P < .05 was significant.

RESULTS: The time to maximum concentration and the mean residence time in pregnancy compared with the postpartum state were not significantly different. During early and late pregnancy, maximum concentration and the last measurable anti–factor Xa activity level were lower than in the nonpregnant state (P < .05). The area under the plasma activity–versus–time curve was significantly lower in pregnancy than in the postpartum state (P < .05).

CONCLUSION: The pharmacokinetics of enoxaparin sodium are significantly different during pregnancy than in the same women when nonpregnant. The observed difference is likely because of increased renal clearance of enoxaparin during pregnancy. This finding has significant implications for appropriate dosing of enoxaparin in pregnancy. (Am J Obstet Gynecol 1999;181:1113-7.)

Key words: Pharmacokinetics, low-molecular-weight heparin, pregnancy

Antithrombotic therapy with heparin is indicated for a variety of conditions during pregnancy. To prevent recurrent thrombosis, women with a history of thromboembolism are given prophylactic doses of heparin during pregnancy. Although 5000 U of unfractionated heparin every 12 hours is usually effective prophylaxis for high-risk surgical patients, changes in the pharmacokinetics and pharmacodynamics of unfractionated heparin during pregnancy make this regimen inadequate.1, 2 During the third trimester of pregnancy, Brancazio et al2 found both a shorter time to peak heparin effect and a lower peak effect after subcutaneous administration of unfractionated heparin in pregnant women compared with nonpregnant women. Barbour et al1 demonstrated that heparin levels were below the therapeutic range for prophylaxis in 14 (100%) of 14 women receiving 5000 U of unfractionated heparin every 12 hours in the first trimester. Even when the dose was increased to 7500 U every 12 hours in the second trimester and 10,000 U every 12 hours in the third trimester, heparin levels were subtherapeutic in 5 (56%) of 9 patients in the second trimester and 6 (47%) of 13 patients in the third trimester. The observed changes in the pharmacokinetics of unfractionated heparin are likely caused by physiologic alterations, such as increased plasma volume, increased glomerular filtration rate, and production of placental heparinase.

Several studies have shown that low-molecular-weight heparins do not cross the placenta in any trimester.3, 4 Low-molecular-weight heparins are at least as effective as unfractionated heparin for thromboprophylaxis and have a lower risk of bleeding, heparin-induced thrombocytopenia, and possibly osteoporosis.5, 6 Because of these advantages, low-molecular-weight heparins are being used with increasing frequency in pregnancy. Like unfractionated heparin, low-molecular-weight heparin is cleared through the kidney and could be subject to changes in pharmacokinetics in pregnancy. We hypothesized that the pharmacokinetics of low-molecular-weight heparin...
heparin would change throughout gestation. If this were found to be true, then regimens found to be effective in nonpregnant patients may not be adequate in those who are pregnant. Therefore we performed the following study to determine the pharmacokinetics of enoxaparin sodium after subcutaneous administration to pregnant women and to compare the pharmacokinetics during and after pregnancy.

**Methods**

Fourteen women with an indication for heparin prophylaxis during pregnancy were asked to participate in this study. Indications for heparin prophylaxis and patient demographics are summarized in Table I. Women with a history of thrombosis in association with an underlying hypercoagulable state (factor V Leiden mutation, antiphospholipid antibody, lupus anticoagulant, protein S or protein C deficiency, or antithrombin III deficiency) were treated with therapeutic doses of anticoagulants and thus were excluded from the study. Women with thrombocytopenia (defined as a platelet count <100,000/µL) or other contraindication to heparin were also excluded from the study. Informed consent, as approved by the University of Pittsburgh and Magee Womens Hospital Institutional Review Boards, was obtained.

Each woman self-administered a single daily subcutaneous injection of 40 mg (4000 U) of enoxaparin sodium. Enoxaparin was supplied in prefilled glass syringes from the manufacturer (Rhone-Poulenc Rorer, Collegeville, Pa). Compliance was monitored every 3 months with syringe counts. In addition to prenatal vitamins, all patients were asked to take a calcium supplement of 500 mg daily. Patients were otherwise healthy and were not receiving long-term medication.

The study participants were admitted to the Clinical Research Center at the University of Pittsburgh for 3 separate 12-hour study periods. The first study period occurred early in pregnancy (12-15 weeks' gestation), the second occurred late in pregnancy (30-33 weeks' gestation), and the third occurred 6 to 8 weeks into the postpartum period. All patients were at least 24 hours from the last enoxaparin dose except for 1 patient late in pregnancy. This patient took the last dose of enoxaparin within 12 hours of the Clinical Research Center admission. The late pregnancy data on this woman were not included in the analysis. An initial blood sample was taken from all the subjects before the administration of 40 mg

### Table I. Demographics of patients

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Height (in)</th>
<th>Weight (lb)</th>
<th>Age (y)</th>
<th>Indication for thromboprophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>64</td>
<td>272</td>
<td>21</td>
<td>Deep venous thrombosis</td>
</tr>
<tr>
<td>2</td>
<td>71</td>
<td>277</td>
<td>21</td>
<td>Deep venous thrombosis</td>
</tr>
<tr>
<td>3</td>
<td>65</td>
<td>127</td>
<td>30</td>
<td>History of recurrent pregnancy loss, positive antiphospholipid antibody</td>
</tr>
<tr>
<td>4</td>
<td>66</td>
<td>120</td>
<td>28</td>
<td>Prior intrauterine fetal death, positive lupus anticoagulant</td>
</tr>
<tr>
<td>5</td>
<td>62</td>
<td>137</td>
<td>30</td>
<td>History of recurrent pregnancy loss, positive lupus anticoagulant</td>
</tr>
<tr>
<td>6</td>
<td>60</td>
<td>130</td>
<td>39</td>
<td>Prior intrauterine fetal death, positive lupus anticoagulant</td>
</tr>
<tr>
<td>7</td>
<td>66</td>
<td>190</td>
<td>39</td>
<td>Prior intrauterine fetal death, positive lupus anticoagulant</td>
</tr>
<tr>
<td>8</td>
<td>60</td>
<td>121</td>
<td>29</td>
<td>Pulmonary embolus</td>
</tr>
<tr>
<td>9</td>
<td>65</td>
<td>130</td>
<td>34</td>
<td>Deep venous thrombosis</td>
</tr>
<tr>
<td>10</td>
<td>62</td>
<td>131</td>
<td>25</td>
<td>History of recurrent pregnancy loss, positive lupus anticoagulant</td>
</tr>
<tr>
<td>11</td>
<td>67</td>
<td>124</td>
<td>30</td>
<td>History of recurrent pregnancy loss, positive lupus anticoagulant</td>
</tr>
<tr>
<td>12</td>
<td>67</td>
<td>170</td>
<td>39</td>
<td>History of recurrent pregnancy loss, positive antiphospholipid antibody</td>
</tr>
<tr>
<td>13</td>
<td>67</td>
<td>139</td>
<td>26</td>
<td>Prior intrauterine fetal death, positive antiphospholipid antibody, positive factor V Leiden mutation</td>
</tr>
<tr>
<td>14</td>
<td>59</td>
<td>148</td>
<td>35</td>
<td>Deep venous thrombosis</td>
</tr>
</tbody>
</table>

### Table II. Pharmacokinetic parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>12-15 weeks' gestation</th>
<th>30-33 weeks' gestation</th>
<th>Postpartum period</th>
<th>Statistical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentration (12 h after dose, IU/mL)</td>
<td>0.09 ± 0.09</td>
<td>0.16 ± 0.10</td>
<td>0.19 ± 0.09</td>
<td>P &lt; .05*†</td>
</tr>
<tr>
<td>Maximum concentration (IU/mL)</td>
<td>0.46 ± 0.08</td>
<td>0.40 ± 0.08</td>
<td>0.57 ± 0.09</td>
<td>P &lt; .05*‡</td>
</tr>
<tr>
<td>Time to maximum concentration (min)</td>
<td>185 ± 66</td>
<td>229 ± 118</td>
<td>192 ± 56</td>
<td>NS</td>
</tr>
<tr>
<td>Area under plasma activity-versus-time curve (IU · mL⁻¹ · min⁻¹)</td>
<td>297 ± 79</td>
<td>384 ± 158</td>
<td>435 ± 118</td>
<td>P &lt; .05*</td>
</tr>
<tr>
<td>Apparent clearance (mL/min)</td>
<td>14.6 ± 4.9</td>
<td>11.7 ± 3.7</td>
<td>10.0 ± 3.6</td>
<td>P &lt; .05*†</td>
</tr>
<tr>
<td>Apparent volume of distribution of drug at steady state (L)</td>
<td>4.0 ± 0.9</td>
<td>3.7 ± 0.9</td>
<td>3.1 ± 1.0</td>
<td>P &lt; .05*‡</td>
</tr>
<tr>
<td>Mean residence time (min)</td>
<td>287 ± 56</td>
<td>325 ± 44</td>
<td>316 ± 32</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values shown are mean ± SEM.

*The value for 12 to 15 weeks' gestation differs from the value for the postpartum period.
†The value for 12 to 15 weeks' gestation differs from the value for 30 to 33 weeks' gestation.
‡The value for 30 to 33 weeks' gestation differs from the value for the postpartum period.
of enoxaparin as a subcutaneous injection. Multiple blood samples (at 30, 60, 90, 120, 150, 180, 210, 240, 300, 360, 420, 480, 600, and 720 minutes after dosing) were obtained over a 12-hour period in tubes containing sodium citrate. The blood was centrifuged immediately to separate plasma, which was then frozen at -4°C until analysis of anti–factor Xa activity. The samples were analyzed in batches for anti–factor Xa activity by amidolytic assay. The minimum detectable limit of this assay was 0.01 anti–factor Xa U/mL. The coefficient of variation for this assay was 6%.

The plasma anti–factor Xa activity measured over the time interval of the study was subjected to noncompartmental pharmacokinetic analysis by using Lagrange (W.J. Jusko, Buffalo, NY) software. Various pharmacokinetic parameters, such as maximum plasma concentration, time to reach maximum plasma concentration, area under the plasma concentration–versus–time curve, apparent clearance, apparent volume of distribution of drug at steady state, and mean residence time were calculated according to standard procedures. SAS version 6.1 (SAS Institute, Cary, NC) software was used for statistical analysis. The data were analyzed by using analysis of variance for repeated measures. The Ryan-Einot-Gabriel-Welsch multiple-range test was used for post hoc comparisons. P < .05 was considered statistically significant.

**Results**

Thirteen women completed all phases of the study. The age of the subjects who participated was 30 ± 6 years (mean ± SD), the height of the subjects was 64 ± 3 in (mean ± SD), and the mean body weight in early pregnancy was 149 ± 42 lb (mean ± SD). Even though all the patients were receiving long-term therapy with enoxaparin, there was no measurable anti–factor Xa activity in any of the plasma samples from the baseline measurement (24 hours after a prior dose) of each study in early and late pregnancy. In contrast, 4 of the 13 postpartum women had measurable anti–factor Xa activity in the baseline sample of the 12-hour study period. Twelve hours after injection, no measurable anti–factor Xa activity was observed in 6 of 13 patients during early pregnancy, 2 of 13 in late pregnancy, and 2 of 13 in the postpartum period.

Table II lists the pharmacokinetic parameters calculated in the study patients over the 3 study periods. The time to maximum concentration and the mean residence time were not significantly different in pregnancy or the postpartum period. The plasma anti–factor Xa activity was generally lower at the last measurable time point, and the maximum concentration achieved was significantly lower in both early pregnancy and later pregnancy than during the postpartum period. The area under the plasma activity–versus–time curve was significantly lower in pregnancy than during the postpartum period (Fig 1).

**Comment**

Low-molecular-weight heparins are actually heparins of low molecular weight that are formed by enzymatic or hydrolytic cleavage with nitrous acid and benzylation after alkaline depolymerization of unfractionated heparin. The mean molecular weight of a low-molecular-
weight heparin is 5000 d (range, 4000-6000 d), whereas
the mean molecular weight of unfractionated heparin is
15,000 d.5 Depending on the specific depolymerization
process used, pharmacologically distinct low-molecular-
weight heparins have been formed that are not inter-
changeable.9 Like unfractionated heparin, low-molecu-
lar-weight heparins exert their anticoagulant activity by
binding antithrombin III, thereby accelerating the inhi-
bition of thrombin (factor IIa) and other serine pro-
teases generated during coagulation, such as factors IXa,
Xa, and XIa, plasmin, and kallikrein.10 Because the abili-
ty to inactivate thrombin is related to molecular size,
low-molecular-weight heparins have a reduced anti-IIa
activity compared with their anti-factor Xa activity. For
this reason, low-molecular-weight heparins do not elevate
the activated partial thromboplastin time. Other advan-
tages of low-molecular-weight heparin over unfraction-
ated heparin include a longer half-life and less protein
binding, which results in greater bioavailability that does
not change at different doses.5 The anticoagulant re-
sponse to low-molecular-weight heparin has been shown
to be quite predictable,11 and thus current recommenda-
tions have not included laboratory monitoring at pro-
phylactic doses in normal weight patients with normal
renal function.

The maximum concentration of enoxaparin and the
time to reach the maximum concentration that were ob-
served in our study subjects in the postpartum period
were similar to measurements observed in other stud-
ies.5,11 Enoxaparin appears to be completely bioavailable
after subcutaneous injection.11 Therefore the apparent
clearance and the apparent volume of distribution calcu-
ated after subcutaneous injection will correspond to the
actual systemic clearance and volume of distribution
of enoxaparin. The systemic clearance of enoxaparin has
been reported to be 0.83 to 1.86 L/h11 and 0.83 ± 0.19
L/h.12 The apparent clearance observed in our study
group ranged from 0.6 to 0.8 L/h. The volume of distribu-
tion of enoxaparin has been reported to be 5.2 to 9.3
L.11 In our subjects the volume of distribution was lower
(3.1-4 L) than what has been reported. The mean resi-
dence time of enoxaparin is reported to be 5.2 to 6.4
hours and is consistent with our findings. Because mean
residence time, which is a measure of the average time a
drug resides in the body, is determined both by clearance
and volume of distribution and because both clearance
and volume of distribution changed in our study pa-
patients, we observed essentially no change in mean resi-
dence time.

Within the patient population studied, the 12-hour
plasma concentration (maximum concentration) and
the area under the plasma activity-versus-time curve
were significantly lower in early pregnancy than post par-
tum. Similarly, the apparent clearance and the apparent
volume of distribution were higher during early preg-
nancy than post partum. When early pregnancy is com-
pared with late pregnancy, maximum concentration is
further decreased in late pregnancy from early pregnancy,
but clearance is also decreased in late pregnancy. Maxi-
mum concentration was the only parameter that was
different between late pregnancy and postpartum stud-
ies.

Our findings are similar to those observed for the low-
molecular-weight heparin dalteparin. Blombak et al13
studied the pharmacokinetics of dalteparin (2500 or
5000 units given once daily) in 17 pregnant women at 32
to 35 weeks' gestation. These investigators compared
their findings with those from historical control subjects
and demonstrated that the peak concentration, time to
maximum concentration, and area under the curve were
lower in the cohort of pregnant patients.

We have shown that the pharmacokinetics of the low-
molecular-weight heparin enoxaparin sodium, like un-
fractionated heparin, change in pregnancy. Because of
normal physiologic changes in pregnancy, such as in-
creased plasma volume, increased glomerular filtration
rate, and production of placental heparinase, enoxa-
parin sodium appears to have a higher clearance and
larger volume of distribution during early pregnancy
compared with the postpartum period in the same
women. Between early and late pregnancy, the maximum
concentration achieved further decreases. This observa-
tion is consistent with increased volume expansion.
However, clearance of enoxaparin apparently decreases
in late pregnancy.

Our study was not designed to evaluate the rela-
tionship of anti-factor Xa activity and clinical outcomes. It is
not known whether a specific minimum level of anti-fac-
tor Xa activity is necessary throughout the day to prevent
thrombosis in pregnancy or whether maintaining a spe-
cific minimum level of anti-factor Xa activity for only a
portion of the day is sufficient. It is also not known
whether thromboprophylaxis in pregnancy is necessary
in some cases because a randomized trial of adequate
sample size comparing prophylactic doses of heparin
with placebo has not been performed. Nevertheless, be-
cause pregnancy is a hypercoagulable state and because
retrospective studies have demonstrated an increased
risk of thrombosis of up to 12% in subsequent pregnan-
cies,14 most clinicians use thromboprophylaxis in preg-
nancy.15 On the basis of prophylactic regimens that have
been shown to be superior to placebo in preventing
thrombosis in high-risk surgical patients, such as those
undergoing total hip replacement,16 maintaining an
anti-factor Xa activity of 0.1 to 0.2 IU/mL has been rec-
ommended.17

In summary, the pharmacokinetics of enoxaparin are
different in pregnancy than in the same women post par-
tum. The pharmacokinetics also change throughout ges-
tation and are different in early and late pregnancy. On
the basis of these data, we conclude that twice-daily dosing of enoxaparin may be necessary to maintain antifactor Xa activity above 0.1 IU/mL throughout a 24-hour period in pregnant women. Optimal dosing throughout the course of pregnancy can be best achieved with periodic monitoring of peak (approximately 3.5 hours after a dose) and predose antifactor Xa activity.

REFERENCES