

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

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Table I. Demographics of patients

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

Table II. Pharmacokinetic parameters

Parameter	12-15 weeks' gestation	30-33 weeks' gestation	Postpartum period	Statistical significance
Concentration (12 h after dose, IU/mL)	0.09 ± 0.09	0.16 ± 0.10	0.19 ± 0.09	$P < .05^{*\dagger}$
Maximum concentration (IU/mL)	0.46 ± 0.08	0.40 ± 0.08	0.57 ± 0.09	$P < .05^{*\dagger}$
Time to maximum concentration (min)	185 ± 46	229 ± 118	192 ± 53	NS
Area under plasma activity-versus-time curve (IU · mL ⁻¹ · min ⁻¹)	297 ± 79	384 ± 158	435 ± 118	$P < .05^*$
Apparent clearance (mL/min)	14.6 ± 4.9	11.7 ± 3.7	10.0 ± 3.6	$P < .05^{*\dagger}$
Apparent volume of distribution of drug at steady state (L)	4.0 ± 0.9	3.7 ± 0.9	3.1 ± 1.0	$P < .05^*$
Mean residence time (min)	287 ± 56	325 ± 44	316 ± 32	NS

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.

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, anticardiolipin 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/mm³) 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

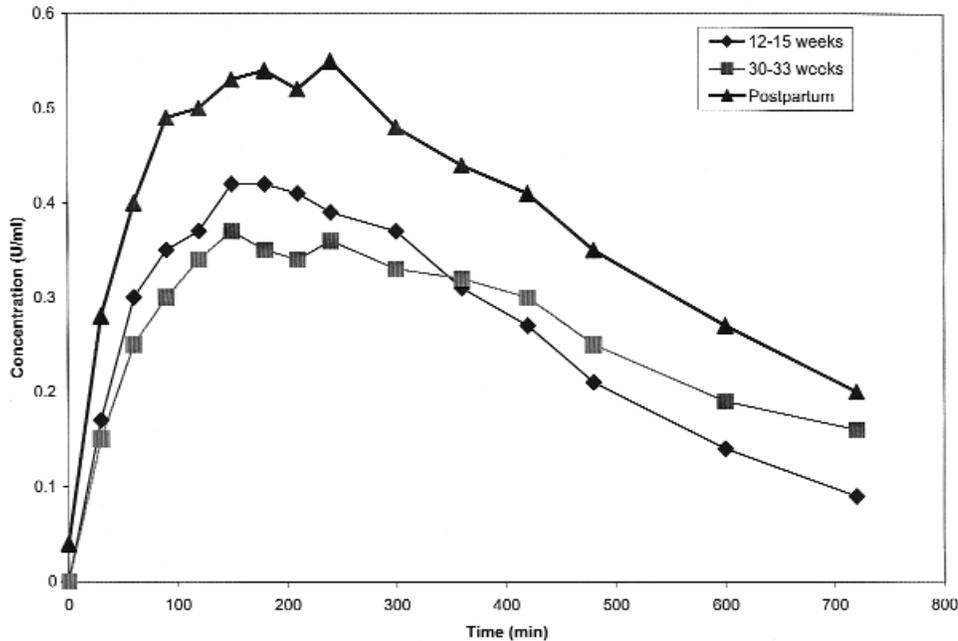


Fig 1. Mean anti-factor Xa activity after subcutaneous injection of 40 mg of enoxaparin sodium (4000 U) during early pregnancy, late pregnancy, and postpartum period in same 13 women.

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.⁷ 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.⁸ 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 \pm SD), the height of the subjects was 64 ± 3 in

(mean \pm SD), and the mean body weight in early pregnancy was 149 ± 42 lb (mean \pm 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 interchangeable.⁹ Like unfractionated heparin, low-molecular-weight heparins exert their anticoagulant activity by binding antithrombin III, thereby accelerating the inhibition of thrombin (factor IIa) and other serine proteases generated during coagulation, such as factors IXa, Xa, and XIa, plasmin, and kallikrein.¹⁰ Because the ability 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 advantages of low-molecular-weight heparin over unfractionated 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 response to low-molecular-weight heparin has been shown to be quite predictable,¹¹ and thus current recommendations have not included laboratory monitoring at prophylactic doses in normal weight patients with normal renal function.

The maximum concentration of enoxaparin and the time to reach the maximum concentration that were observed in our study subjects in the postpartum period were similar to measurements observed in other studies.^{5, 11} Enoxaparin appears to be completely bioavailable after subcutaneous injection.¹¹ Therefore the apparent clearance and the apparent volume of distribution calculated 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 distribution 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 residence 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 patients, we observed essentially no change in mean residence 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 partum. Similarly, the apparent clearance and the apparent volume of distribution were higher during early preg-

nancy than post partum. When early pregnancy is compared with late pregnancy, maximum concentration is further decreased in late pregnancy from early pregnancy, but clearance is also decreased in late pregnancy. Maximum concentration was the only parameter that was different between late pregnancy and postpartum studies.

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 unfractionated heparin, change in pregnancy. Because of normal physiologic changes in pregnancy, such as increased plasma volume, increased glomerular filtration rate, and production of placental heparinase, enoxaparin 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 observation is consistent with increased volume expansion. However, clearance of enoxaparin apparently decreases in late pregnancy.

Our study was not designed to evaluate the relationship of anti-factor Xa activity and clinical outcomes. It is not known whether a specific minimum level of anti-factor Xa activity is necessary throughout the day to prevent thrombosis in pregnancy or whether maintaining a specific 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, because pregnancy is a hypercoagulable state and because retrospective studies have demonstrated an increased risk of thrombosis of up to 12% in subsequent pregnancies,¹⁴ most clinicians use thromboprophylaxis in pregnancy.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 recommended.¹⁷

In summary, the pharmacokinetics of enoxaparin are different in pregnancy than in the same women post partum. The pharmacokinetics also change throughout gestation 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 anti-factor 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 anti-factor Xa activity.

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