Comparison of Anti-Xa Levels in Obese and Non-Obese Pediatric Patients Receiving Treatment Doses of Enoxaparin

Ashley A. Richard, PharmD[1], Shelly Kim, PharmD[1], Brady S. Moffett, PharmD, MPH[1], Lisa Bomgaars, MD[2], Donald Mahoney, Jr., MD[2], and Donald L. Yee, MD[2]

Objective To determine if using actual body weight to dose enoxaparin in obese pediatric patients results in higher anti-Xa levels compared with non-obese pediatric patients.

Study design This was a retrospective case-matched study of obese and non-obese pediatric patients receiving treatment doses of enoxaparin in a tertiary care children's hospital. Patients were included if they were initiated on treatment doses of enoxaparin, had appropriate anti-Xa levels drawn, and were between 2 and 18 years of age. Patients with renal insufficiency, hyperbilirubinemia, goal anti-Xa level <0.5 or >1 unit/mL, or receiving mechanical circulatory support were excluded. Obese patients who met study criteria were matched on a 1:1 basis with non-obese patients.

Results All baseline characteristics were similar except for body mass index percentile (98.2 ± 2 vs 48.7 ± 15, $P < .01$). Obese patients had higher initial anti-Xa levels (0.67 ± 0.27 vs 0.53 ± 0.24 unit/mL, $P = .028$). Over time, obese patients required a lower mean dose to achieve therapeutic anti-Xa levels than non-obese patients (0.81 ± 0.19 vs 1.1 ± 0.4 mg/kg, $P = .005$).

Conclusions The mean initial anti-Xa level was higher in obese pediatric patients compared with non-obese pediatric patients, but a dosage adjustment was not required. Obese patients may need closer monitoring over time to avoid supratherapeutic levels and possible bleeding events. *(J Pediatr 2013;162:293-6)*.

The results from the 2007-2008 National Health and Nutrition Examination Survey estimated that 17% of children and adolescents between the ages of 2 and 19 were obese.[1] Obese patients are at risk for many medical problems, such as hypertension, heart disease, and thromboembolism, and obesity can alter the pharmacokinetic properties of medications.

A recent study has shown that the rate of venous thromboembolism in children has increased by about 70% from 2001-2007.[2] Studies in adults have shown that dosage adjustments of the commonly used anticoagulant drug enoxaparin may be necessary in special populations such as those with obesity and renal failure and one small case series suggests dose modifications are needed for obese children receiving the drug for prophylaxis.[3-8] There are recommendations for changes in enoxaparin dosing schedules for patients with renal failure, but not for obese patients, either adult or pediatric. Current practice in children is to dose enoxaparin based on actual body weight.[4] However, enoxaparin is a water soluble drug that does not readily distribute into adipose tissue.[4,9] Using actual body weight in obese patients could lead to an unintentional overdose, increasing risk for serious bleeding events and patient harm. Enoxaparin is considered a high-alert medication by the Institute for Safe Medication Practices due to the heightened risk of causing significant harm when used in error.[10] Overall, the above considerations coupled with the significant increase in use of enoxaparin in children underscores the importance of evaluating the dosing of this high risk medication in obese pediatric patients.[2,9]

The primary objective of this study was to determine if using actual body weight to dose enoxaparin in obese pediatric patients results in higher anti-Xa levels compared with non-obese pediatric patients. Secondary objectives were to determine if obese pediatric patients experience more bleeding events than non-obese pediatric patients or a greater incidence of supratherapeutic (>1 unit/mL) anti-Xa levels while receiving treatment doses of enoxaparin. Other secondary endpoints included determining the average initial dose (mg/kg) based on actual body weight, frequency of dose changes required to maintain target anti-Xa levels during the study observation period, and the average of all doses (mg/kg) resulting in a therapeutic level during the study observation period (average therapeutic dose).

Methods

A retrospective case-matched study was performed to evaluate anti-Xa levels in pediatric patients who received treatment doses of enoxaparin (1 mg/kg subcutaneously twice daily).[11] Approval was obtained from the Institutional Review Board for Baylor College of Medicine and Affiliated Institutions. Pharmacy

BMI	Body mass index
CrCl	Estimated creatinine clearance

From the [1]Department of Pharmacy, Texas Children's Hospital, and the [2]Department of Pediatrics, Hematology/Oncology Section, Baylor College of Medicine, Houston, TX

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databases at Texas Children's Hospital were queried from July 2007-June 2010 to identify patients who had received treatment doses of enoxaparin.

As defined by the Centers for Disease Control and Prevention, a patient was considered obese when the body mass index (BMI) was greater than or equal to the 95th percentile for age and sex.[12] A patient was considered non-obese if their BMI was between the 25th and 75th percentile for age and sex. This IQR of BMI was chosen to ensure that neither overweight (85th-94th percentile BMI) nor underweight patients (<5th percentile BMI) were chosen as controls. Obese patients who met inclusion criteria were matched on a 1:1 basis with non-obese patients based on age (±2 years), sex, and acuity of care (intensive care unit vs non-intensive care unit) at initiation of therapy. A total of 90 days of enoxaparin therapy or complete duration of therapy if the course was less than 90 days was analyzed for each patient. Estimated creatinine clearance (CrCl) was calculated by the Schwartz equation.[13]

Patients were included if they were between the ages of 2 and 18 years, started on treatment doses of enoxaparin, and had appropriate peak anti-Xa levels drawn (4-6 hours after the second dose of enoxaparin). Inter-assay and intra-assay coefficient of variations for the anti-Xa assay ranged from 2.8%-5.9% and 2.5%-4.6%, respectively (STA Rotachrome Heparin 8 kit; Diagnostica Stago, Parsippany, New Jersey). Patients excluded were those with goal anti-Xa levels <0.5 or >1 units/mL, renal insufficiency (CrCl <75 mL/min/1.73 m^2) as defined by the modified pediatric risk, injury, failure, loss of kidney function, and end-stage kidney disease criteria, elevated bilirubin levels (unconjugated bilirubin ≥6 mg/dL), as this can interfere with the assay used to determine anti-Xa levels, or receiving mechanical circulatory support while receiving enoxaparin.[14] Data collection included demographic information, indication for use of enoxaparin, CrCl at initiation of therapy, enoxaparin dose, changes in enoxaparin dose, and appropriately drawn anti-Xa levels.

The study was powered to detect a mean difference in anti-Xa level of 0.3 units/mL between obese and non-obese pediatric patients. To have an alpha of 0.05 and a power of 80%, approximately 25 patient pairs were required. Patient demographic, disease state, and enoxaparin dosing information were summarized with descriptive statistics. Comparisons between obese and non-obese patient groups were made using Student *t* test for continuous data, χ^2, and Fisher exact test for categorical data, and the Mann-Whitney U test for nonparametric data.

Results

Thirty matched pairs were identified during the study period. No significant differences were noted between groups in age, sex, indication for enoxaparin, or baseline CrCl (Table I). In virtually all cases (n = 59), enoxaparin was used to treat a thromboembolic event; in one obese patient (n = 1), the indication for enoxaparin use was prevention of thromboembolism due to a thrombophilic risk profile that included factor V Leiden, protein C deficiency, and homocysteinemia.

Table I. Baseline data

	Obese (n = 30)	Non-obese (n = 30)	*P* value
Age (y)	11.6 ± 4.4	11.4 ± 4.3	Not applicable
Male	53%	53%	Not applicable
Weight (kg)	74.2 ± 38.1	40.1 ± 15.6	<.01
Height (cm)	146 ± 29	144 ± 24	.80
Body surface area (m^2)	1.7 ± 0.6	1.3 ± 0.3	<.01
BMI percentile (%)	98.2 ± 2	48.7 ± 15	<.01
Estimated baseline CrCl (mL/min/1.73m^2)	162 ± 43	155 ± 49	.58

The initial dose of enoxaparin was similar between obese and non-obese patients (Table II). One obese patient was >183 kg (the largest patient in the dataset) and received an initial dose of 170 mg. Obese patients had a significantly higher initial anti-Xa level compared with non-obese subjects (0.67 ± 0.27 vs 0.53 ± 0.24 unit/mL; $P = .028$); however, the mean initial anti-Xa level in both groups was within the therapeutic range (Table II).

There was no difference in the frequency of dose changes or supratherapeutic levels between obese and non-obese patients (Table II). Of patients with supratherapeutic levels, obese patients had a higher mean supratherapeutic level (Table II). Only one bleeding event was identified in an obese patient who came to the emergency department for bleeding gums and was subsequently discharged to continue on enoxaparin. During the entire study observation period, the average therapeutic dose (average dose resulting in a therapeutic anti-Xa level) was lower in obese compared to non-obese patients (0.81 ± 0.19 vs 1.1 ± 0.4 mg/kg; $P = .005$). Over the course of therapy, both obese and non-obese patients required lower doses of enoxaparin to maintain a therapeutic anti-Xa level (Figure).

Discussion

The hypothesis for this study was that obese patients would demonstrate higher anti-Xa levels when dosed by actual body weight on a per kilogram basis compared with non-

Table II. Results

Category	Obese (n = 30)	Non-obese (n = 30)	*P* value
Initial dose (mg/kg)	0.93 ± 0.16	0.98 ± 0.19	.22
First appropriately drawn anti-Xa level (unit/mL)	0.67 ± 0.27	0.53 ± 0.24	.028
Average therapeutic dose (mg/kg)	0.81 ± 0.2	1.1 ± 0.4	.005
Dose changes during study period (n = total)	68	67	
Increase (%)	26 (38%)	35 (52%)	.12
Decrease (%)	42 (62%)	32 (48%)	
Supratherapeutic levels during therapy			
Patients (%)	21 (70%)	14 (47%)	.12
Supratherapeutic level (unit/mL)	1.21 ± 0.17	1.08 ± 0.08	<.01