FONDAPARINUX PROPHYLAXIS AND ANTI-FACTOR XA CONCENTRATIONS IN PATIENTS WITH MORBID OBESITY

Venous thromboembolism (VTE) incorporates deep venous thrombosis (DVT) and pulmonary embolism, potentially fatal conditions that affect approximately 300,000 patients and can lead to 100,000 deaths per year. Research has shown that VTE occurrence is increased 2 to 3 fold in obese individuals. Up to 50% of VTEs occur during the course of a hospital stay. Prophylactic use of unfractionated heparins, low molecular weight heparins, and the pentasaccharide fondaparinux has successfully reduced the risk of inpatient VTE by up to 68%. Historically, there has not been a focus on obese patients in the studies utilizing these injectable agents for prevention of VTE, nor have there been any comparisons of responses in non-obese versus obese patients. Additionally, some studies have concluded that prophylactic dosing with low molecular weight heparins or unfractionated heparins may not be adequate for prophylaxis in obese patients. This issue of CLIPS briefly summarizes a retrospective cross-sectional study that investigates the utility of fondaparinux for VTE prevention in morbidly obese patients. If you need further information, please contact the Samford University Drug Information Service at (205)726-2659.


METHODS

• Retrospective cross-sectional study of medical records of all morbidly obese patients (n= 79) admitted to the University of New Mexico Hospital from May 2009 to March 2010 receiving fondaparinux for VTE prophylaxis
• Patients included: ≥18 years of age, receipt of fondaparinux 2.5 mg subcutaneously daily for VTE prophylaxis, BMI ≥40 kg/m², estimated creatinine clearance of >30 mL/min, at least one peak fondaparinux anti-factor Xa concentration after four or more doses of fondaparinux (reference range 0.3 – 0.5 mg/L based on pharmacokinetic information from GlaxoSmithKline)
  o Methodology for determining anti-factor Xa concentrations was validated by comparing ex vivo samples from patients receiving fondaparinux and plasma samples containing fondaparinux with results from three other laboratories
• Patients excluded: those whose samples for obtaining anti-factor Xa concentrations were collected inappropriately
• Primary endpoint: percentage of morbidly obese patients receiving standard prophylactic doses of fondaparinux who achieved an anti-factor Xa concentration of 0.3 – 0.5 mg/L
• Approved by the human research review committee at the University of New Mexico Health Sciences Center

RESULTS

• 81 anti-factor Xa concentrations from 79 patients were determined, of which 47 concentrations from 45 patients met inclusion criteria. Of those 47 concentrations:
  o 20 (43%) were within the target anti-factor Xa range (0.3 – 0.5 mg/L)
  o 22 (47%) were below 0.3 mg/L
  o 5 (11%) were above 0.5 mg/L
• There were no significant differences in age, weight, BMI, number of doses received before sample collection or length of hospital stay in any of the above three groups.

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However, renal function differed significantly among the three groups.

- Patients above the target anti-factor Xa range (>0.5 mg/L) had higher mean ± S.D. serum creatinine (1.12 ± 0.45 mg/dL) than those within the range (0.77 ± 0.19 mg/dL) or below the range (0.68 ± 0.20 mg/dL); \( P = 0.021 \).
- Significant differences in renal function among the three groups were also reflected by the estimated creatinine clearance. Patients above the range (>0.5 mg/L) had lower mean ± S.D. estimated creatinine clearance (79.6 ± 25.0 mL/min) than those within the range (135.6 ± 49.4 mL/min) or those below the range (179.5 ± 73.2 mL/min); \( P = 0.001 \).

According to stepwise linear multiple-regression analysis, significant predictors of anti-factor Xa concentration included serum creatinine \( (P = 0.005) \), sex \( (P = 0.004) \), BMI \( (P = 0.009) \), and number of fondaparinux doses before sample collection \( (P = 0.022) \). Serum creatinine concentration accounted for 22% overall variance in anti-factor Xa concentration; sex, 9.6%; BMI, 4.7%; and number of fondaparinux doses before sample collection, 6.2%.

DISCUSSION

- Research has shown an increased risk of VTE associated with obesity.
- It has been proposed that conventional prophylactic doses of anti-thrombotic medications such as heparin and low-molecular weight heparins may not be enough to prevent VTE occurrence in obese patients.
- Four clinical trials have shown increased efficacy in regard to anti-factor Xa levels with higher, weight-based doses of enoxaparin and dalteparin.
- Phase III trials of fondaparinux for VTE prevention revealed that the clearance of fondaparinux increased by 9% for every 10 kg increase in weight, which could theoretically lead to lower anti-factor Xa levels in heavier patients.
- This retrospective cross sectional study is the first to retrospectively evaluate whether standard dosing of fondaparinux for VTE prophylaxis in morbidly obese patients is appropriate based on anti-factor Xa concentrations.
- Only 53% of the morbidly obese \( (\text{BMI} \geq 40 \text{ kg/m}^2) \) patients in this study receiving standard doses of fondaparinux achieved anti-factor Xa levels at or above the minimum of the target range for VTE prophylaxis \( (0.3 \text{ mg/L}) \).
- Statistically significant correlations were evident between anti-factor Xa levels and renal function, sex, the number of fondaparinux doses before sample collection, and BMI.
  - Fondaparinux is renally eliminated, which supports the significance of renal function on sample levels.
  - Women had higher mean anti-factor Xa concentrations than men.
  - Correlation of the number of doses before sample collection and anti-factor Xa levels suggests accumulation.
  - BMI results suggest that plasma clearance of fondaparinux increases as weight increases.

SUMMARY

- Dose response relationships of fondaparinux in morbidly obese patients are poorly established.
- This retrospective chart review demonstrated that only 53% of morbidly obese patients receiving standard dosing of fondaparinux for VTE prophylaxis were within the target anti-factor Xa range.
- The results of this study suggest that many morbidly obese patients receiving standard prophylactic doses of fondaparinux are not reaching the target anti-factor Xa range for VTE prophylaxis.
- The clinical significance of low factor Xa inhibition in morbidly obese patients is unknown. Future studies are needed to determine if insufficient anti-factor Xa activity in morbidly obese patients resulting from standard prophylactic doses of fondaparinux will translate into clinical outcomes.
- The evidence provided in this study is not sufficient to recommend increasing prophylactic dosing of fondaparinux in patients with morbid obesity. Additional information is needed to determine what dosage adjustments, if any, are necessary to achieve both appropriate anti-factor Xa levels and clinical outcomes in patients with morbid obesity.

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