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Research Article

Low-Molecular-Weight-Heparin as Thromboprophylaxis: a Dosage Problem in Obese Patients

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Abstract

Background: Prophylaxis with fixed doses of low-molecular-weight heparin (LMWH) is standard procedure to reduce the risk of venous thromboembolism after surgery. Patient studies have rarely been stratified for body weight. There is evidence to suggest that lack of sufficient levels of anti-factor X_a-activity (anti-X_a) in morbidly obese patients on LMWH. Anti-X_a is used as a measurement of antithrombotic activity. The objective of the present study was to see, for obese patients, whether body weight-adjusted dosing of enoxaparin results in anti-X_a levels comparable to those of a standard fixed dose of normal weight patients. **Material and Methods:** Subcutaneous injections of enoxaparin 0.3 mg/kg and 0.6 mg/kg were administered to 10 morbidly obese volunteers (median body weight 127 kg). Plasma anti-X_a was measured at defined intervals for 10 hours after injection. Reference values for anti-X_a were obtained from a former study where a fixed dose of 40 mg enoxaparin was given to subjects with different body weights. **Results:** Body weight dosing with 0.6 mg/kg enoxaparin yields levels of anti-X_a in the same range as in normal weight patients who receive the recommended fixed dose of 40 mg. **Conclusion:** Body weight-adjusted dosing may be considered in perioperative thromboprophylaxis with LMWH in obese patients.

Keywords: low-molecular-weight heparin, obesity, surgery, thrombosis, thromboprophylaxis

Introduction

Venous thromboembolism is one of the major causes of mortality after surgery and one of the strongest patient-specific risk factors is obesity, a factor rapidly becoming more prevalent. Obese individuals have an increased percentage of fat per kilogram bodyweight and blood flow in adipose tissue is lower compared to lean body mass

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(Cheymol, 2000). Thus, proper dosing regimens need to be established.

Pharmacological thromboprophylaxis is widely used, and recommendations for peak and through levels of the substitute end-point "anti-factor X_a-activity" (anti-X_a) have been given (Levine et al., 1989). Renal function and thus elimination has been taken into account in several studies, but rarely body weight/obesity. The recommendations of the Medical Products Agency in Sweden, give risk classification of the patient, renal function and patient age as the variables that indicate dose adjustments (FASS, 2013). Only recently body weight regarding standard thromboprophylaxis for the morbidly obese has been added in Swedish and American PDR (FASS, 2013, PDR, 2013).

In a previous study, we measured anti-X_a after fixed doses in patients with varying body weights, and found a negative linear correlation with body weight. Neither the peak activity nor the area-under-curve observed in the normal-weight subjects were reached in the obese, and we concluded that the recommended doses were inadequate in heavy patients (Frederiksen et al., 2003).

The objective of the present study was to test the hypothesis that, by using a weight-dependent dose it would be possible to get the same anti-X_a activity in obese patients as in normal-weight subjects.

Patients and Methods

Ten patients scheduled for gastric bypass surgery were recruited after informed consent. Six were women, four were men. All invited participants concluded the study. Body weights ranged between 108 and 147 kg (median 127 kg); Body mass indices ranged between 35 and 58 kg/m^2. No patient was planned for surgery within the next two-week period.

Each of our subjects was tested twice, the minimum interval between injections was set at five days and the order of injections was randomised. At each test a subcutaneous dose of enoxaparin (Klexane®, Roerig, Sweden) was given. As estimated from data from our former study, (Frederiksen et al., 2003) the tested lower dose (0.3 mg/kg) corresponds to the standard dose recommendation for low-risk patients of 20 mg, while the higher dose (0.6 mg/kg) corresponds to the 40 mg recommended standard dose for high risk patients.

Blood samples for anti-X_a were drawn before enoxaparin-injection and at one-hour intervals up to six hours post-injection, then at eight and ten hours. Samples were collected in tubes with 0.5 ml 0.129 mmol/l sodium citrate solution. Tubes were immediately centrifuged at 2000g for 20 minutes; plasma was separated and frozen at - 80° C. After all subjects had been tested twice, samples were analysed in a batch using the Behring Coagulation System (Behring Diagnostica AB, Stockholm Sweden) and anti-X_a was measured using Coamatic® Heparin (Chromogenix Instrumentation Laboratory S.p.A., Milano, Italy).

Some individuals had a (low) spontaneous anti-X_a at baseline, as previously described (Bendz et al., 1999). We subtracted this activity from all further samples from these individuals; incremental values were used in the further analyses.

Data were stored in Microsoft Excel® and analysed using Graph Pad Prism 5. The study was approved by the local Ethics Committee in Lund.

Results

All ten subjects completed the study. Anti-X_a was plotted for the two different doses as a function of time for individual patients as well as for the group (summarized in figure 1). Anti-X_a peaked after approximately four hours. Peak values for 0.6 mg/kg were twice those for 0.3 mg/kg and the difference was statistically significant at all time-points.

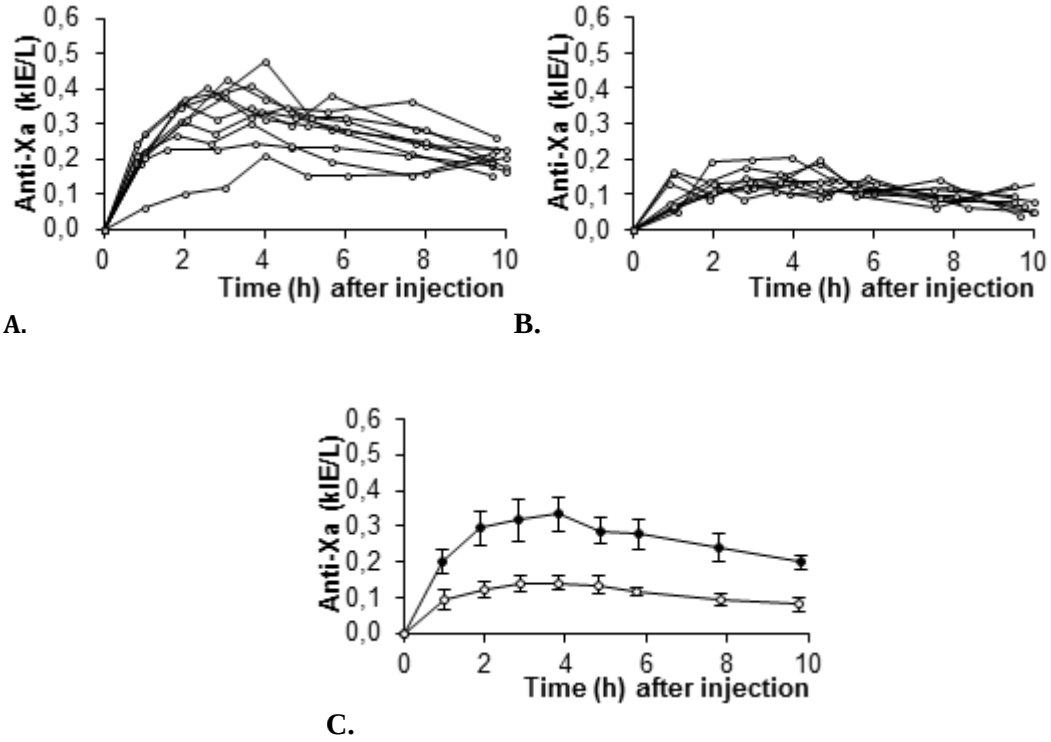

Figure 1. Panel A: Incremental plasma levels of anti-Xa-activity with time after injection of enoxaparin 0.6 mg/kg. Panel B: Incremental plasma levels of anti-X_a-activity with time after injection of enoxaparin 0.3 mg/kg. Panel C: Mean and 95% CI for values in panels A and B. p> 0.001 at all time-points after baseline.

The area under the curve (AUC) for the 10 hours studied, was calculated for each individual and dose, and plotted as a function of body weight (fig 2). By giving weight-adjusted enoxaparin, anti-X_a had no correlation to total body weight; a dose of 0.6 mg/kg gave roughly a doubling of the total anti-X_a compared to a dose of 0.3 mg/kg

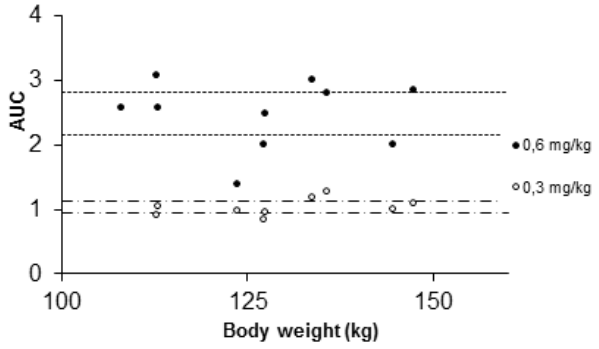

Figure 2. Area under the curve (AUC) for the time period studied, as a function of body weight for each individual patient in the two dosage groups. Mean (95% CI): For 0.3 mg/kg 1.0 (CI 0.95 – 1.1 (dashed lines)) and for 0.6 mg/kg 2,5 (CI 2.2 – 2.8 (dotted lines)).

In an earlier separate set of measurements, we compared the anti-X_a after administration of a fixed 40 mg dose of enoxaparin to patients and volunteers with varying body weights (Frederiksen et al., 2003). Previously unpublished data from that experiment are given in figure 3, in the same form as figure 1 – individual and mean values but up to 18

hours post injection. A standard dose of 40 mg in heavy-weight patients did not elicit a rise in plasma anti-X_a of the magnitude seen in normal-weight individuals.

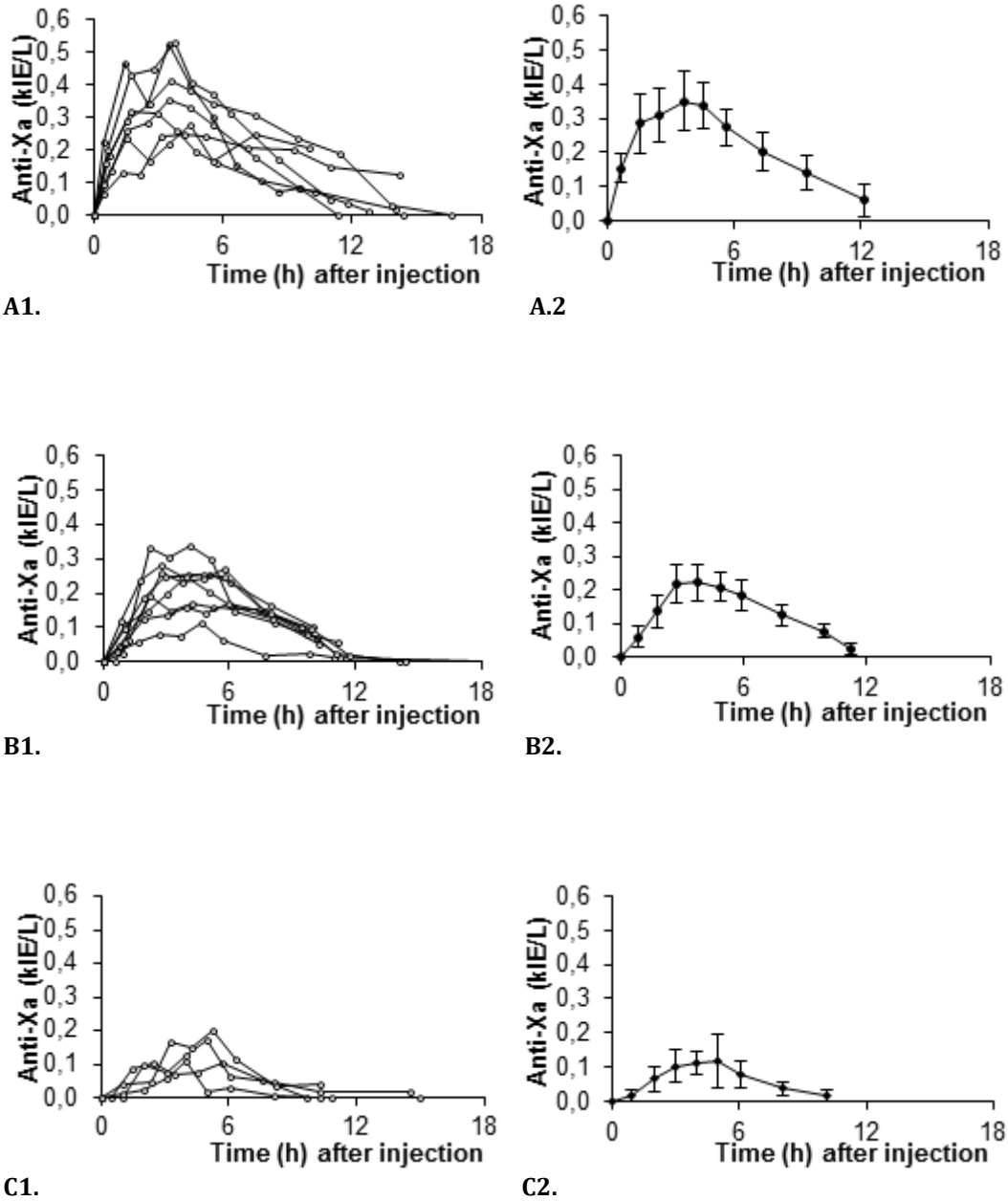

Figure 3. Incremental plasma levels of anti-X_a-activity with time after injection of a fixed dose of 40 mg of enoxaparin. (Non-published data from the study by Frederiksen et al. 2003). Individual values in upper diagrams, mean and 98% CI plotted in lower diagrams.

As seen in figure 4, over time and regardless of body weight, anti-X_a was identical in normal-weight patients given fixed standard dosing and in obese patients given 0.6 mg/kg.

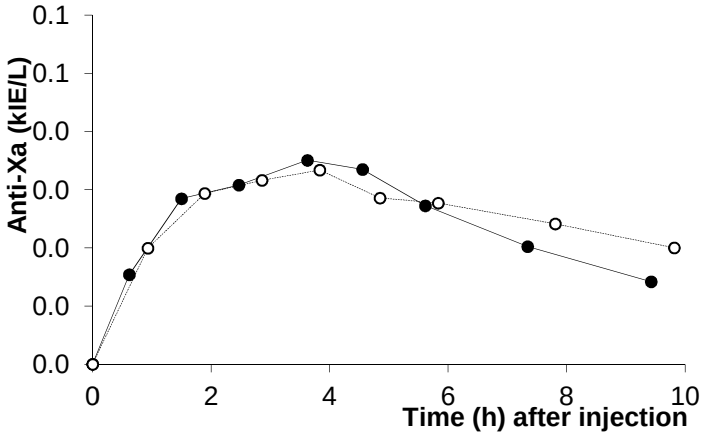

Figure 4: Comparison of mean plasma levels of anti-factor-X_a with time after the injection of 0.6 mg/kg in obese patients (solid line) and a fixed dose of 40 mg to normal weight patients (dashed line; non-published plot from Frederiksen et al. 2003).

The AUC values in figure 5 demonstrate that all patients given the weight-adjusted dose of 0.6 mg/kg had values corresponding to those achieved in the normal-weight patients given a fixed dose of 40 mg.

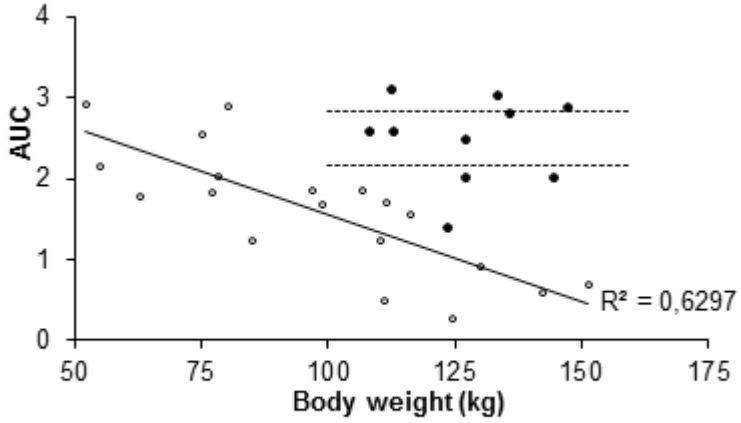

Figure 5: Area under curve (AUC) values for individual patients given 40 mg enoxaparin (open circles and trend line). Closed circles represent AUC values for individual patients given 0.6 mg/kg enoxaparin. Dashed lines mark 95% CI for AUC-means in the 0.6 mg/kg group. The 40 mg data are from our previous study (Frederiksen et al. 2003, reprinted with permission).

Discussion

With increasing prevalence of obesity in the population, all surgeons need proper regimens to handle the weight-specific problems arising. Thromboembolic disease is a feared complication to surgery. Bariatric surgical procedures are associated with a 30-day overall mortality rates of 0.1–2% (Buchwald et al., 2004, Flum et al., 2005). The large Scandinavian study SOReg reports an even lower 90 day figure, 0.04% (11/25038)

(Stenberg et al, Annals of Surgery, In press) The incidence of postoperative deep venous thrombosis or symptomatic venous thromboembolism has been stated to be 0.8–2.4% (Westling et al., 2002, Prystowsky et al., 2005, Podnos et al., 2003, Eriksson et al., 1997). Retrospective analyses have reported an incidence of fatal pulmonary embolism after obesity surgery of 0.2–0.3% (Eriksson et al., 1997, Sapala et al., 2003). The American Society of Bariatric Surgery Registry has given pulmonary embolism as the most common cause of 30-day postoperative death and states that prophylaxis is recommended for all patients and should be continued until patients are ambulatory. The following guidelines have been given by the American Association of Clinical Endocrinologists, the Obesity Society, and American Society for Metabolic & Bariatric Surgery: Sequential compression devices and subcutaneous unfractionated heparin 5000 IU or LMWH should be initiated shortly (within 30–120 min) before bariatric surgery and repeated every 8–12 h postoperatively until patient is fully mobile. IVC filter is suggested to be reserved for higher risk obese patients (e.g., pulmonary hypertension or hypercoagulable state) (Mechanick et al., 2008). Even with thromboprophylaxis obese patients are at higher risk of thrombosis (Rocha et al., 2006).

Although laparoscopy causes less surgical trauma compared to open surgery (Schauer and Sirinek 1995), laparoscopy has been associated with reduced venous return and thereby possibly increased risk of thrombosis due to pneumoperitoneum and reversed Trendelenburg position (Nguyen et al., 2003).

LMWHs are normally given in either of two standard doses, the choice of which is determined by assessment of patients being at normal or at high risk of thromboembolic disease. Dosing intervals have been discussed in ICU patients, but standard practice in elective abdominal surgery, is once every 24h.

The recommended doses of LMWH stem from large, well-designed studies not commenting the effect on morbidly obese patients being performed in a bariatric surgery setting (Kakkar et al., 1993, Group 1997). The proper dosage in heavy-weight patients is still not scientifically determined, although different fixed doses have been compared in the obese setting (Simone et al., 2008, Rowan et al., 2008).

Given the relative rarity of pulmonary embolism, a study comparing fixed to weight-related dosing of LMWH, needs a substitute endpoint. Anti-X_a has been accepted as that endpoint, although questioned on correlation with thromboembolic complications in a paper on ICU-patients
(Rutherford et al., 2005). Steady-state enoxaparin activity levels are well predicted by single-dose pharmacokinetics and peak and through values for desired activity are known. We have established plasma anti-X_a values for our laboratory in normal weight patients given recommended doses (Frederiksen et al., 2003). The values so obtained are taken to be the desired range. In the present set of experiments we compared the effect on plasma anti-X_a of two weight-adjusted dosing regimens.
In order to strengthen statistics, the study was designed to enable each patient to serve as its own control for the weight-adjusted two doses. Laboratory accuracy was enhanced by performing a batch analysis of deep frozen samples. Although the number of patients is small, differences in anti-X_a between doses are large. For all patients the 0.6 mg/kg AUC-values fell within the reference range established for our laboratory when giving 40 mg enoxaparin once daily to normal-weight patients (fig 5). The dose of 0.3 mg/kg body-weight for obese patients did not reach the reference values, neither for peak activity (fig 1 and 3), nor for AUC values (fig 2 and 5).

Since regimens with fixed doses every 24h are standard practice in abdominal surgery, our study could suggest that new recommendations for dosing LMWH may be indicated in obese patients. Our findings are clearly supported by a recent study on morbidly obese, medically ill patients (Rondina et al., 2010). The present data were recruited in obese patients, who were heavy for body height but also heavy in absolute terms. Further studies are indicated to see whether the implications of this study can be transferred to heavy, non-obese patients.

In summary obese patients do not reach the same level of thromboprophylaxis as normal weight subjects, if standard fixed doses of LMWHs are given, at least not as measured

using the surrogate variable anti-factor X_a. For enoxaparin, a weight-adjusted regimen of 0.6 mg/kg body-weight is suggested but clinical studies in the perioperative setting are needed to assess the risk of post-operative bleeding.

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