The influence of morbid obesity on the pharmacokinetics and pharmacodynamics of drugs in adolescents and adults : focus on propofol and nadroparin.

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Anti-Xa levels 4 h after subcutaneous administration of 5,700 IU nadroparin strongly correlate with lean body weight in morbidly obese patients

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Obesity Surgery 2012, published online

Abstract

Background

Morbidly obese patients (BMI > 40 kg/m^2) are at increased risk for venous thromboembolism, especially after surgery. Despite limited evidence, morbidly obese patients are often administered a double dose of nadroparin for thromboprophylaxis compared to non-obese patients. The aim of this study was to evaluate the influence of different body size descriptors on anti-Xa levels after a double dose of nadroparin (5,700 IU) in morbidly obese patients.

Methods

In 27 morbidly obese patients with a mean total body weight (TBW) of 148 kg (range 107 – 260 kg), anti-Xa levels were determined peri-operatively until 24 h after administration of a subcutaneous dose of 5,700 IU of nadroparin.

Results

Anti-Xa level 4 h after administration (A_{4h}, mean 0.22 ± 0.07 IU/ml) negatively correlated strongly with lean body weight (LBW) (r = -0.66 (p<0.001)), moderately with TBW (r = -0.56 (p=0.003)) and did not correlate with BMI (r = -0.26 (p=0.187)). The area under the anti-Xa level-time curve from 0 to 24 h (AUA_{0-24h}, mean 2.80 ± 0.97 h*IU/ml) correlated with LBW (r = -0.63 (p=0.007)), but did not correlate with TBW (r = -0.44 (p=0.075)) or BMI (r = -0.10 (p=0.709)).

Conclusion

Following a subcutaneous dose of nadroparin 5,700 IU, A_{4h} and AUA_{0-24h} were found to negatively correlate strongly with LBW. From these results, individualized dosing of nadroparin based on LBW should be considered in morbidly obese patients.

Introduction

Currently more than 30% of the US population is obese (Body Mass Index (BMI)>30 kg/m²) and 2.8% of adult men and 6.9% of adult women are morbidly obese (BMI>40 kg/m²) (1). Consequently, there is a marked increase of this special group of patients presenting for various types of surgery, including bariatric surgery. In obese patients, the relative risk for venous thromboembolism (VTE) is more than doubled compared to non-obese patients, and even five times higher in obese patients with an age of 40 years or younger (2).

Low-molecular-weight heparins (LMWH) have shown to substantially reduce the risk for VTE by inactivating clotting factor Xa (3-4). Compared to unfractionated heparin, LMWH have a more favourable benefit-risk ratio and a more predictable dose-response relationship (5). In the ACCP guidelines, LMWH are recommended for prophylactic use in morbidly obese patients albeit without any specific recommendation for the dose in this special population (5-6). These guidelines recommend to monitor the effect of LMWH in morbidly obese patients using anti-Xa levels (6). Since LMWH are a mixture of polysaccharides that includes biologically inactive species, it is not possible to measure LMWH levels directly (4). The commonly reported prophylactic range of anti-Xa levels for non-obese patients is 0.2 – 0.5 IU/ml 4 h after administration (7).

In the lack of specific dosing guidelines for dose adjustment of LMWH in morbidly obese patients, different body size descriptors have been proposed, such as total body weight (TBW) (8) and BMI (9-10). However, in clinical practice the prophylactic dose of LMWH is often doubled in morbidly obese patients resulting in 5,700 IU nadroparin (11). The aim of this study was to evaluate the influence of different body size descriptors on anti-Xa levels following a dose of 5,700 IU of nadroparin in morbidly obese patients. In this study, anti-Xa levels 4 h after administration (A_{4h}) and the area under the anti-Xa level-time curve from 0 to 24 h ($AUA_{0\text{-}24h}$) were considered and studied for a correlation with LBW (12), TBW and BMI.

Materials and methods

Patients

Twenty-seven morbidly obese patients scheduled to undergo laparoscopic gastric banding or gastric bypass surgery were enrolled in two prospective studies (ClinicalTrials.gov identifier cohort 1: NCT01097148 and cohort 2: NCT01309152). Patients were included if they were between 18 and 60 years old, had an American Society of Anesthesiologists (ASA) physical status classification of II or III, a normal renal and liver function as assessed by routine laboratory testing, and a BMI of over 40 kg/m² at the day of screening. Exclusion criteria included a BMI lower than 35 kg/m² at the day of surgery, LMWH administration within 48 h preceding surgery, pregnancy, breast feeding, epilepsy and known allergy for propofol, soy bean oil or egg lecithin. Both study protocols were approved by the hospitals ethics committee and written informed consent was signed by each participating patient.

Procedure

In both cohorts, before induction, an antecubital infusion line, an indwelling arterial blood pressure line and a three-lead ECG were installed. No pre-anaesthetic medication was given, and all patients were fasting for 6 h before surgery to minimize the risk of aspiration during induction. Following a propofol bolus injection of 350 mg, intravenous fentanyl and cefazolin were given in fixed doses of 250 µg and 2 g, respectively, followed by 5,700 IU (0.6 ml) nadroparin subcutaneously administered in the thigh. Anaesthesia was maintained with continuous infusions of propofol and remifentanil after induction of anaesthesia according to routine clinical practice.

Blood sampling and analytical methods

Blood samples for determination of anti-Xa-levels were collected before induction of anaesthesia (t=0), at 10, 30, 60, 90, 120, 180, 240, 300 and 420 minutes after nadroparin dosing and the next morning within 24 h after administration in cohort 1, and before induction of anaesthesia, 120 and 240 minutes after nadroparin dosing and the next morning within 24 h after administration in cohort 2. Blood samples were collected in 3.2% buffered sodium citrate containing tubes and were immediately stored on ice until centrifugation. All samples were centrifuged at 4 °C within one hour after collection to obtain plasma samples, and stored at –80 °C until analysis within 1 month after collection. Plasma levels of anti-Xa activity were measured with a STA-Rack Evolution (Diagnostica Stago, Asnières, France) using an anti-Xa clotting assay (StaClot®Heparin, Diagnostica Stago, Asnières, France). The rate of chromophobe appearance at 405 nm was measured. Calibration occurred with eight concentrations of nadroparin (STA® Multi Calibrator) in normal pooled plasma. The calibration curve was found to be linear between 0.00 and 1.60 IU/ml. The within assay and among assay precision (coefficient of variation) were 4.7 % and 4.9 %, respectively. Regression analysis was used to determine the calibration curve values from

which the experimental values were obtained.

Data analysis

Statistical software (PASW Statistics 19.0 for Windows; IBM, Chicago, IL, US) was used for statistical analysis. Continuous data were expressed as mean ± SD. To study the association between anti-Xa level 4 h after administration (A_{4h}) and the area under the anti-Xa level-time curve from 0 to 24 h (AUA_{0-24h}) and different body size descriptors (TBW, BMI and LBW (12)) the Pearson's correlations coefficient (r) was calculated. A $p<0.05$ was considered significant. The area under the anti-Xa level-time curve from 0 to 24 h (AUA_{0-24h}) was calculated using the linear trapezoidal method (13) with estimating the levels at t = 24 h using the last two or three samples. Lean body weight, which is considered to closely approximate fat free mass (12), was calculated using formulas of Janmahasatian et al, for men: (9,270 * TBW (kg)) / (6,680 + 216 * BMI) and for women: (9,270 * TBW (kg)) / (8,780 + 244 * BMI) (12).

Results

Patients and Data

Twenty-seven morbidly obese patients with a mean TBW of 149 kg (range 107 - 260 kg) were enrolled and a total of 240 blood samples were available. Nineteen patients were included from cohort 1, and eight patients from cohort 2. All demographic characteristics of the morbidly obese patients from cohort 1, cohort 2 and total study population are provided in Table I.

Anti-Xa levels 4 h after administration (A_{4h}) were available in all 27 patients of cohort 1 and 2. While in cohort 2 there were insufficient data to calculate the area under the anti-Xa level-time curve from 0 to 24 h (AUA_{0-24h}), AUA_{0-24h} could be analyzed in 17 patients of cohort 1.

Anti-Xa levels

Mean anti-Xa levels 4 h after administration (A_{4h}) after the administration of 5,700 IU nadroparin in those morbidly obese patients and the area under the anti-Xa level-time curve from 0 to 24 h (AUA_{0-24h}) are shown in Table II. Thirteen morbidly obese patients (48%) showed anti-Xa-levels below the prophylactic range of 0.20 - 0.50 IU/ml .

Figure 1 shows that A4h strongly correlated with LBW (r = -0.66, $p<0.001$), moderately correlated with TBW (r = -0.56, p=0.003) and did not correlate with BMI (r = 0.26, p=0.187). Figure 2 demonstrates that AUA_{0-24h} strongly negatively correlated with LBW (r = -0.78, p=0.007) and did not correlate with TBW (r = -0.44, p=0.075) or BMI (r = -0.10, p=0.709).

Figure 3 shows the results of both A_{4h} and AUA_{0-24h} from this study together with previously reported values in the literature of non-obese (14-19) and (morbidly) obese patients (11, 19) versus nadroparin dose. The figure demonstrates that in non-obese patients there is a linear dose-response curve for both A_{4h} and AUA_{0-24h}. The results of this study after administration of 5,700 IU nadroparin in morbidly obese patients show an A_{4h} and AUA_{0-24h} that are lower than would be expected from these dose-response relationships. Similar results are shown for anti-Xa levels in obese patients that were previously reported (Figure 3).

Table I *Patient characteristics of twenty-seven morbidly obese patients receiving 5,700 IU nadroparin subcutaneously.*

Parameter	Total study population (mean (SD))	Cohort 1 (mean (SD))	Cohort 2 (mean (SD))
Patients (n)	27	19	8
Age (y)	44 (9)	45 (10)	40 (6)
Sex (M / F)	10 / 17	9 / 10	1 / 7
TBW (kg)	149 (32)	153 (35)	140 (23)
IBW (kg)	67 (10)	68 (11)	64 (7)
LBW (kg)	71 (14)	74 (15)	66 (9)
BMI (kg/m²)	49 (10)	50 (10)	47 (6)

BMI = body mass index; F = female; IBW = ideal body weight (28); LBW = lean body weight(12); M = male; SD = standard deviation; TBW = total body weight

Table II *Mean anti-Xa levels 4 h after administration (A_{4h}) and mean area under the anti-Xa level-time curve from 0 to 24 h (AUA_{0-24h}) after 5,700 IU of nadroparin (prophylactic range of anti-Xa levels 4 h after administration is 0.2 – 0.5 IU/ml for non-obese patients (7)).*

	Mean (SD)	Number
A_{4h} (IU/mL)	0.22 ± 0.07	27
A_{4h} percentage below prophylactic range (%)	48%	
AUA_{0-24h} (h * IU/mL)	2.80 ± 0.97	17

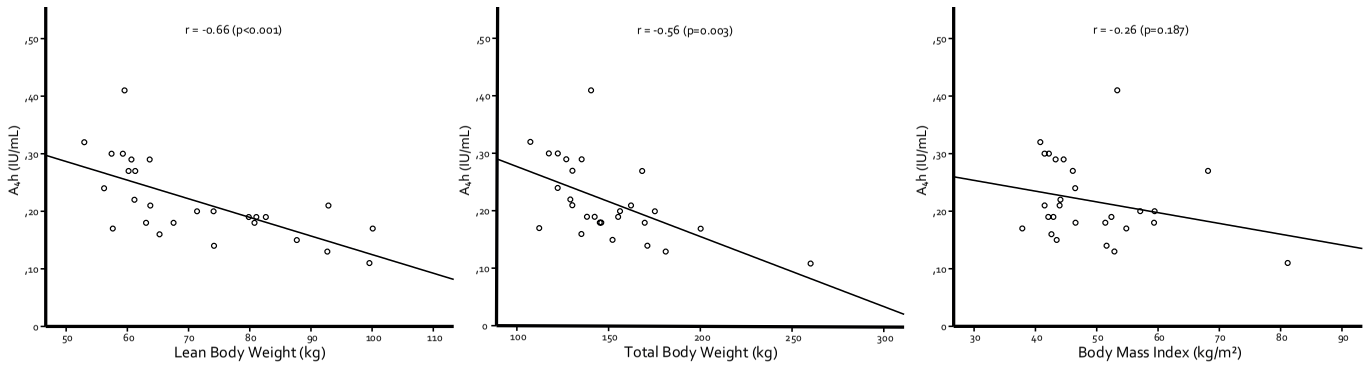

Figure 1 *Anti-Xa levels 4 h after administration (A_{4h}) versus lean body weight (12), total body weight and body mass index in 27 morbidly obese patients after administration of 5,700 IU of nadroparin subcutaneously, including Pearson's correlation coefficient (r).*

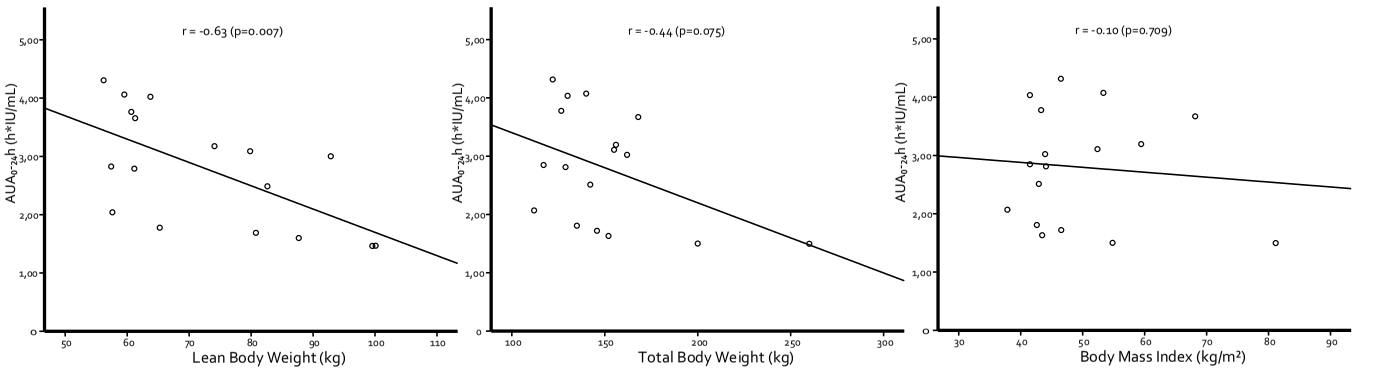

Figure 2 *The area under the anti-Xa level-time curve from 0 to 24 h (AUA_{0-24h}) versus lean body weight (12), total body weight and body mass index in 17 morbidly obese patients after administration of 5,700 IU of nadroparin subcutaneously including Pearson's correlation coefficient (r).*

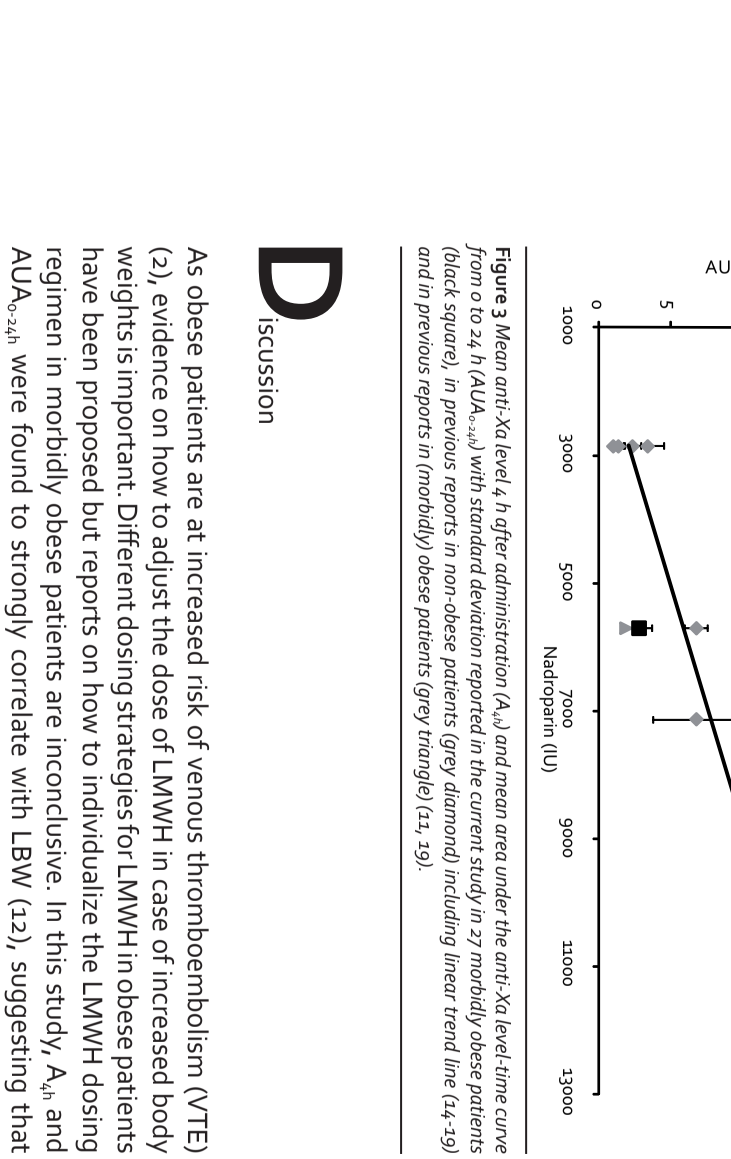

Figure 3 *Mean anti-Xa level 4 h after administration (A_{4h}) and mean area under the anti-Xa level-time curve from 0 to 24 h (AUA_{0-24h}) with standard deviation reported in the current study in 27 morbidly obese patients (black square), in previous reports in non-obese patients (grey diamond) including linear trend line (14-19) and in previous reports in (morbidly) obese patients (grey triangle) (11, 19).*

Discussion

As obese patients are at increased risk of venous thromboembolism (VTE) (2), evidence on how to adjust the dose of LMWH in case of increased body weights is important. Different dosing strategies for LMWH in obese patients have been proposed but reports on how to individualize the LMWH dosing regimen in morbidly obese patients are inconclusive. In this study, A_{4h} and AUA_{0-24h} were found to strongly correlate with LBW (12), suggesting that

this body size descriptor deserves further study in morbidly obese patients.
As stated before, measurement of anti-Xa levels is recommended in morbidly obese patients (6, 20) in absence of established dosing protocols for LMWH for these patients. Although no range has been established in morbidly obese patients and morbidly obese patients are at increased risk for VTE (2), it seems rational to aim for at least anti-Xa levels of 0.2 - 0.5 IU/mL, which is the reported prophylactic range for non-obese patients (7). Half of the morbidly obese patients in this study (48 %) showed anti-Xa levels below this window, suggesting increased doses might be necessary. In addition, since the relationship between anti-Xa levels and the occurrence of bleedings (21) or VTE (22) is unknown, studies on this relationship in morbidly obese patients receiving prophylaxis with LMWH are urgently needed to define the optimal window of anti-Xa levels in morbidly obese patients.
It has been reported before by Heizmann et al. that a linear increase in nadroparin dose does not result in a linear increase in maximum anti-Xa levels after 4 h and AUA levels in obese patients and that dosing should not be based on TBW (19). The reported anti-Xa levels were, however, not correlated to other body size descriptors and, therefore, no conclusions could be drawn on how to optimize nadroparin doses in obese patients. Similarly, for enoxaparin, peak anti-Xa levels in morbidly obese patients were not found to correlate with TBW or BMI (8). A dosing regimen based on LBW instead of TBW would seem to make more sense since it has a non-linear increase with height and TBW. It has therefore been proposed before for the therapeutic dose of enoxaparin for patients weighing more than 100 kg (23). LBW, representing fat free mass in individuals, can be measured with bioelectrical impedance analysis (BIA) or dual-energy x-ray absorptiometry (DXA). To estimate LBW, the formula by Janmahasatian et al. (12) is the most commonly used method as it was found to provide good predictive performance of the Fat Free Mass measured with bioelectrical impedance analysis (BIA) or dual-energy x-ray absorptiometry (DXA) (12). In this study, we investigated the correlation between LBW (12) and anti-Xa levels and $AUA_{0\text{-}24h}$. As shown in Figure 3, there is a substantial influence of excessive body weight on anti-Xa levels after subcutaneous administration of nadroparin in morbidly obese patients as the results of morbidly obese patients are well below the line for non-obese patients. These results seem in accordance with the correlation described in this study between LBW (12) and A_{4h}. As LMWH are mainly distributed over vascular tissue and blood, an explanation for this relation for A_{4h} may be the non-linear increase of plasma volume with body weight (24). Since there are no reports available indicating a reduced biological availability of LMWH in obese patients (25-26), it may be anticipated that the lower $AUA_{0\text{-}24h}$ in morbidly obese patients compared to non-obese patients is caused by an increased glomerular filtration in morbidly obese patients (27) which increases nadroparin clearance. These hypotheses need clarification in future studies.
In conclusion, both anti-Xa levels 4 h after administration and the area under the anti-Xa level-time curve from 0 to 24 h after subcutaneous administration of nadroparin in morbidly obese patients were negatively correlated strongly with LBW (12). From these results, individualized dosing on the basis of LBW should be considered in morbidly obese patients.

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