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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Treatment of pulmonary embolism in an extremely obese patient

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Abstract

The low-molecular-weight heparins are effective as initial therapy for pulmonary embolism (PE) in a weight-based dosing regimen up to known total body weights of 160 kg.
The present case reports an extremely obese man of 252 kg (body mass index (BMI) 74 kg/m^2) with PE who was treated with tinzaparin, dosed on a total body weight of 160 kg.
Morbid obesity defined as a BMI higher than 40 kg/m2 is becoming more common in general practice, but there are no evidence-based drug dosing strategies for these patients.
This case demonstrates the successful use of a maximum dose of 28,000 anti-Xa international units of tinzaparin for an extremely obese patient with proven PE, instead of the accepted doses of 175 IU/kg, as bridge therapy to a coumarin.

Case report

A 47-year-old male patient weighing 252 kg, who was scheduled for bariatric surgery later that year, was admitted to our hospital because of chest pain radiating to his left arm and acute dyspnea. The pain was not exercise-related and treatment with nitroglycerin did not relieve the symptoms. The patient's weight increased over the last few years; the actual body mass index (BMI) was 74 kg/m^2 at presentation. His medical history included gout, systemic hypertension, primary hyperventilation syndrome, appendectomy and cholecystectomy. The patient acknowledged being a smoker (25 cigarettes/day). There was no history of deep vein thrombosis or pulmonary embolism (PE).

Upon arrival in the emergency room, his blood pressure was 160/75 mm Hg with a pulse rate of 75 bpm, a temperature of 37.2 °C and an arterial oxygen saturation of 94% with support of 1 L/min of oxygen. When the patient was breathing room air the saturation dropped to 84 %. The laboratory results showed increased D-dimer levels of 2,749 µg/L (0-250 µg/L), a pro-B-type natriuretic peptide value of 75 pg/mL (< 88 pg/mL), a glucose level of 6.1 mmol/L and a serum creatinine level of 72 µmol/L. After medical examination, there were no clinical signs of deep venous thrombosis, like leg pain or other signs of thrombophlebitis in the lower limbs or presence of varices expect edema in both ankles due to morbid obesity.

Pulmonary embolism was suspected and a lung ventilation and perfusion scan was performed because the patient was unable to pass the CT-scan. The perfusion scan performed with 192 MBq (instead of 100 MBq) macroaggregates of albumin labelled with Technetium-131 (TechneScan® LyoMAA) and the ventilation scan performed with Krypton-81m gas confirmed the diagnosis of PE, with more than two lung segments showing no perfusion and normal ventilation.

According to the local protocol, the patient was treated with tinzaparin. Due to overall stability of the patient and in accordance to the guidelines of the American College of Chest Physicians, no further interventions were considered (1). Tinzaparin was started 3 h after admission with a dose of 175 IU anti-Xa/kg subcutaneously, according to the labelled dose of tinzaparin, which resulted for this total body weight of 252 kg in a total dose of 42,000 IU (2.7 ml). In consultation with the Department of Clinical Pharmacy, it was then decided to continue with a once daily dose of 28,000 IU anti-Xa a day (175 IU/kg dose capped at 160 kg instead of 252 kg), because 175 IU/kg based on a total body weight of 160 kg had previously been reported to be safe and effective and because it was assumed that a total body weight above 160 kg would not influence the clearance nor the volume of distribution of tinzaparin any further (2-4). In addition to this dosing advice, anti-Xa activity measurement was proposed to monitor the effect of this dose, thereby preventing concentrations lower than 0.5 IU/mL 4-5 h after the s.c. dose (5) and targeting at a concentration of 1-2 IU/mL 4-5 h after the s.c. dose at day 3 of treatment (6). 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 anti-Xa assay standard calibration curve of tinzaparin ranged from 0 to 1.5 IU/mL. The within assay and among assay precision (coefficient of variation) were 4.7% and 4.9%, respectively. Also on day 1, 6 mg of acenocoumarol was administrated orally and adjusted based on the measured prothrombin time (PT/INR) (Table I).

During and following treatment with tinzaparin and acenocoumarol, the patient was relieved from his pain after 2 days and supplemental oxygen could be stopped after 4 days because he recovered from his dyspnea symptoms. Anti-Xa levels remained within the predetermined target values (Table I). No bleeding, bruising events or other complications occurred. He was discharged after 5 days when an adequate PT/INR > 2.0 was established (Table I). Both acenocoumarol and tinzaparin (for 3 more days) were continued after discharge. Three days after his discharge, the patient was readmitted because of constipation. During this readmission anti-Xa levels were measured after his last dose of tinzaparin (Table I). Five months after this event, the patient was stable without clinical signs of venous tromboembolism, and no additional coagulation testing was used to determine the presence of any ongoing thrombotic activity. Gastric bypass surgery was performed after which the patient recovered and was discharged.

Discussion

Obesity is an increasing health risk worldwide, with the US, UK and Australia recording a prevalence in adults of around 20 % (7). Approximately 4.8 % of the overall population are considered to be morbidly obese with a BMI higher than 40 kg/m2 (8-9). While in the overall population in the US pulmonary embolism (PE) resulted in approximately 200,000 deaths in 20 years (10), prospective data indicate that obesity is associated with an increased risk for a PE in women (11). In the treatment and prevention of PE, low-molecular-weight heparins (LMWH) have proven to be effective (12-13) and tinzaparin once daily is labelled for the treatment of PE. According to

Table I *Tinzaparin and acenocoumarol doses and anti-Xa and PT/INR levels in the 252 kg patient.*

Day	Time (h)	Tinzaparin (IU)	Tinzaparin (IU/kg)	anti-Xa (IU/mL)	Acenocoumarol (mg)	PT/INR
1	2:00					
1	5:00	42,000	166.3			
1	20:00			0.54 (= A)		
1	22:00	28,000	110.9		6	
2	8:00			0.72 (= B)		1.1
2	16:00	28,000	110.9			
2	22:00				4	
3	8:00	28,000	110.9			
3	13:40			1.34 (= C)		
3	22:00	28,000	110.9		2	
4	8:00					1.8
4	22:00	28,000	110.9		3	
5	8:00					2.1
5	22:00	28,000	110.9		3	
6	8:00					
6	17:00	28,000	110.9		3	
7	8:00					
7	17:00	28,000	110.9		2	
8	8:00					3.1
8	20:00	28,000	110.9		2	
9	8:00					2.7
9	14:00			0.28 (= D)		
9	20:00				2	
10	8:00					2.3

the label, tinzaparin dose corresponds to 175 IU/kg and should be based on the actual total body weight of the patient (14).

However, no dosing guidelines are available for the treatment of PE in extremely obese patients. Previously, reports of tinzaparin provided information that a safe and effective use of 175 IU/kg total body weight could only be guaranteed for total body weights up to 160 kg (2). A similar linear weight-based dosing regimen using once daily dalteparin has been proposed before, but total body weights were restricted to a maximum of 190 kg and the indication was treatment of venous tromboembolism instead of PE (14-15). Also for enoxaparin linear weight-based schemes have been reported up to a total body weight of 165 kg for the treatment of acute venous thromboembolism (16), which is similar to the proposed weight-based regimen for nadroparin in the prophylaxis of tromboembolism in obese patients up to a total body weight of 152 kg (17). The patient described in this report weighs over 250 kg, which results in a very high dose when total body weight is used for calculation of the dose, thereby potentially leading to bleeding risks. Therefore a fixed dose, capped at a 160 kg was considered, similar to a previously proposed dosing regimen for enoxaparin, e.g. a standard dose of 40 mg for a BMI up to 50 kg/m^2 and 60 mg enoxaparin for a BMI higher than 50 kg/m^2 (18). For the same reasons of safety issues, more recently, a dosage based on lean body weight (LBW) has been proposed (19), which results in lower dosages compared to calculations based on total body weight in extremely obese patients such as in our case. LBW is based on sex, weight and height and does not linearly increase with total body weight and is therefore expected to correlate better with the clearance of LMWHs (20). However, this study was performed in only 11 patients with a maximum total body weight of 120 kg, and therefore, the wide introduction of LBW as a basis for dosing in extremely obese patients may be too early. Beside safety issues, the final decision to administer a dose capped at a total body weight of 160 kg was also based on reports in obese patients that total body weight is not a significant predictor for tinzaparin clearance (3). Additionally, based on the pharmacokinetic properties of LMWH, the volume of distribution of tinzaparin was not expected to have a linear relationship with total body weight in extremely obese patients (e.g. BMI > 50 kg/m^2 or total body weight > 150 kg) as tinzaparin does not expected to distribute in adipose tissue. As a result of all these considerations, it was concluded that the use of a linear weight-based dosing regimen in extremely obese patients may potentially lead to overdosing and higher risks of bleeding (6), and therefore in our case a dose cap at 160 kg was chosen together with anti-Xa measurements.

A possibility to evaluate the efficacy of a proposed dosing regimen is to monitor anti-Xa levels. Although the relationship between anti-Xa levels and efficacy or safety of LMWH treatment is not entirely clear (6, 21), levels

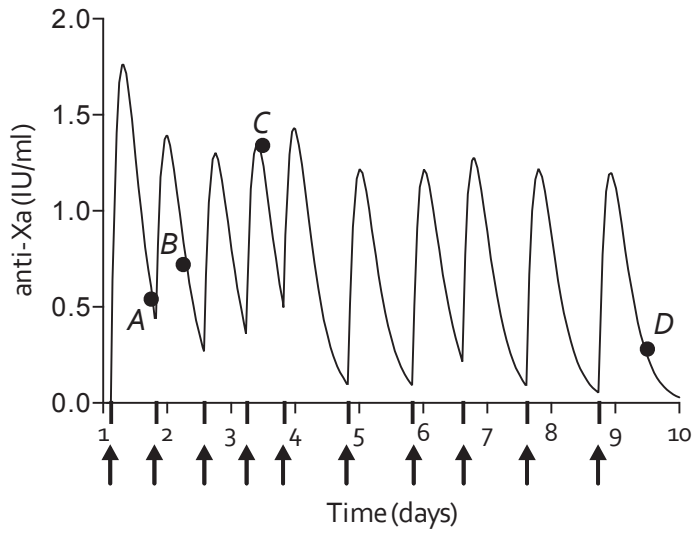

Figure 1 *Observed anti-Xa levels (circle) in the 252 kg patient with line of best fit according to a one-compartment model (line) and dosing records of tinzaparin (arrow). Measured anti-Xa levels are plotted in the figure (A, B, C and D), for details see table 1. Day 1 is the day the patient arrived at our hospital.*

of 1.0- 2.0 IU/mL have been suggested for treatment of PE with once daily tinzaparin, when measured 4-5 hours after the subcutaneous injection on day 3 (22). Additionally, for enoxaparin, it has been demonstrated that anti-Xa concentrations lower than 0.5 IU/mL, 4-6 h after administration of the second dose, resulted in an increased risk of mortality at 30 days (5). Results from a study in obese volunteers with a maximum total body weight of 165 kg (BMI of 61 kg/m^2) show that the maximum concentration of anti-Xa was 0.81 IU/mL (0.76 – 0.86 IU/mL) 4 h after subcutaneous administration of a single dose of 175 IU/kg tinzaparin (2), which seems to be in accordance with the previously mentioned target concentrations. Also in our patient, we monitored anti-Xa concentrations in order to evaluate whether our assumptions on tinzaparin behaviour in extremely obese patients were correct. We found that all anti-Xa concentrations were within the predetermined target values (see Table I).

For the purpose of the current report, we retrospectively fitted the anti-Xa measurements of the patient from Table I using a one-compartment pharmacokinetic model (iterative two-stage Bayesian fitting using MWPharm 3.50, Mediware, The Netherlands) with pharmacokinetic parameters of tinzaparin in non-obese patients (23). It was found that the line very adequately described the observed anti-Xa levels in our patient, which seems to confirm our assumption that tinzaparin does not distribute any further over adipose tissue in extremely obese patients (Figure 1; pharmacokinetic parameters of anti-Xa in this patient were found to be 1.14 L/h for clearance, 5.28 L for volume of distribution with an assumed bioavailability of 59%). From Figure 1 it can also be concluded that, based on measurements at day 1, pharmacokinetic modelling can be applied to estimate whether the target concentration, which is defined for day 3, will be reached, as the line of best fit very adequately describes the observed anti-Xa concentrations. However, it should be realized that there is a highly degree of uncertainly because the fitted data is based on 4 measurements of anti-Xa of only one extremely obese patient, and therefore, more research is needed to confirm these findings.

In summary, this case describes the successful treatment of PE in a 252 kg patient (BMI 74 kg/m2) with tinzaparin in a fixed dose of 28,000 IU per day, corresponding to 175 IU/kg for a total body weight of 160 kg. Larger studies are needed to confirm whether this fixed dose of tinzaparin is effective and safe in extremely obese patients.

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