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Enoxaparin Dosing in Obese Patients

Presentation Objectives

- Apply pharmacokinetic changes caused by obesity to enoxaparin dosing
- Explain pharmacology of enoxaparin
- Make dosing adjustments in obese patients undergoing enoxaparin therapy

Patient Case

- A 57 yof admitted to CCF on 08/29/10 for abdominal wall mass resection
- PMH: PE (post surgery 09'), morbid obesity, MI (04'), HTN, T2DM,
- Ht: 67", Wt: 410lbs (186.4kg), Scr: 1.0
- IBW: 61.6kg, ABW: 111.5kg
- Est. CrCl (ABW): 109.3 ml/min
- H/H: 31.0/10.0, Plt: 172
- Allergies: none

Patient Case, Meds PTA

- Warfarin 10mg PO (dose adjusted by PCC)
- NPH Insulin 10 units SQ hs
- Metformin 1000mg PO bid
- Pydridoxine (B-6) 100mg PO bid
- Glipizide 10mg PO bid
- Simvastatin 20mg PO hs
- Atenolol 100mg PO daily

Patient Case, Hospital Course

- 08/29/10: Pt admitted, UFH drip started
  - UFH used inpatient d/t concern of subtherapeutic anticoagulation with enoxaparin if done outpatient
- 09/01/10: Abdominal mass resection surgery
- 09/02/10: Erythema at incision site
  - Started cephalexin 500mg PO q6h
- 09/04/10: Incision cellulitis/erythema worsened
  - Started vancomycin 1.5g IV q12h
- Continue pt on UFH drip to bridge to warfarin or send home on enoxaparin bridge?

Obesity Epidemiology

- Obesity = BMI ≥ 30 (morbid obesity ≥ 40)
- Incidence increasing rapidly since 1980
- More prevalent amongst minority populations
  - African American, Hispanic, Native American
- Overweight
  - 32.2% of adults are overweight/obese
  - 17.1% of teenagers are overweight/obese
- Morbid obesity
  - 2.8% of men and 6.8% of women [1]

Note: all statistics are from 2004

Obesity Pharmacologic Effects

- Increased Vd
  - Especially lipophilic drugs
  - Increased length of distribution phase
- CL remains largely unchanged
  - Adipose tissue has no intrinsic extraction properties
  - Primarily dependent on LBW [2]

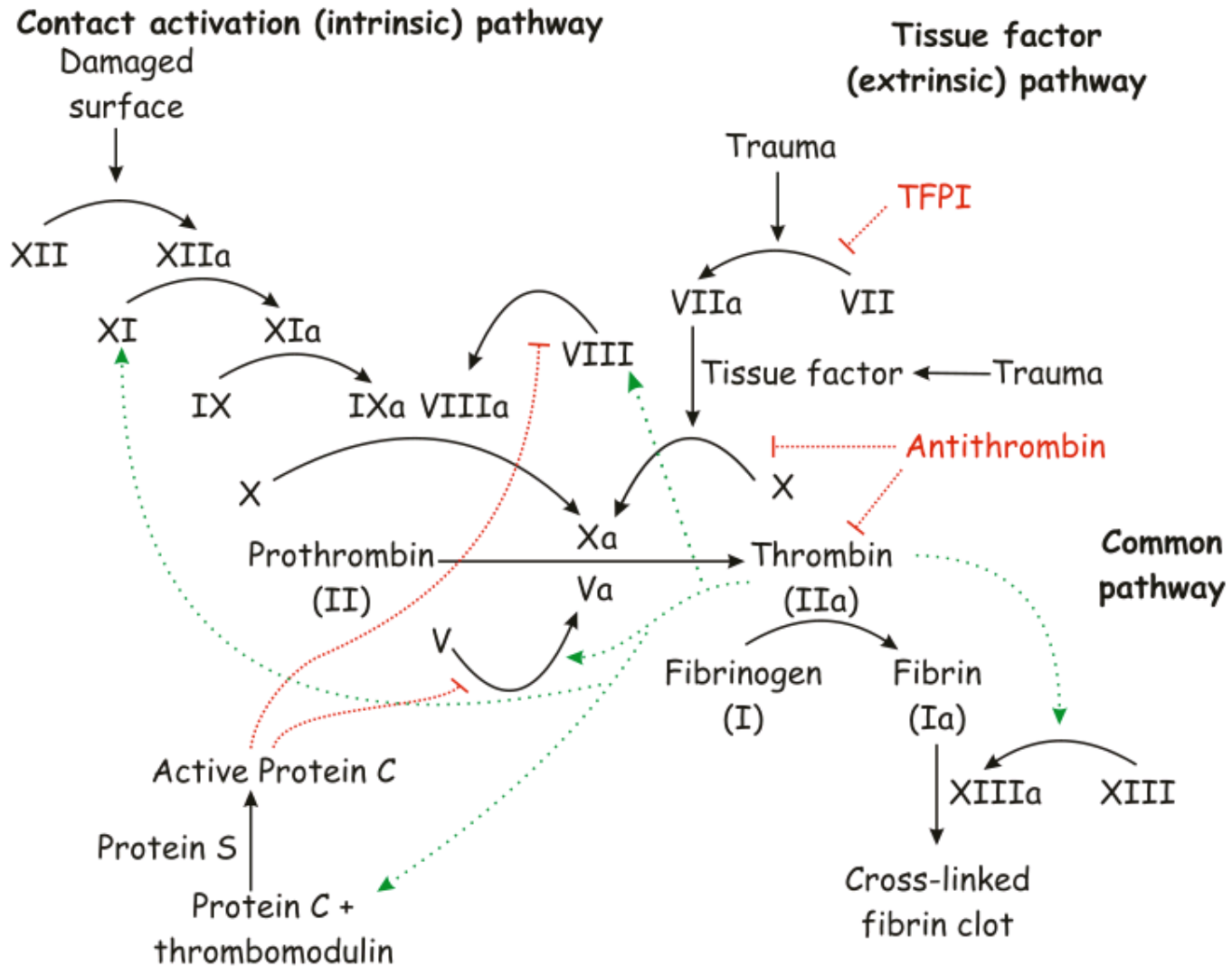
Enoxaparin Pharmacology

- FDA approved indications:
  - ACS (UA, NSTEMI, STEMI)
  - DVT/PE prophylaxis and treatment
    - Both inpatient and outpatient
- MOA: inhibition of factor Xa
  - Cannot catalyze thrombin-antithrombin reaction d/t short chain length (< 18 monosaccharides long)
  - Higher ratio of factor Xa: factor IIa activity [3]

Enoxaparin Pharmacology (cont.)

- PK/PD:
  - OOA: 3-5hrs
  - DOA: 12hrs
  - T1/2: 4.5-7hrs
  - Vd: 4-6 liters (roughly equivalent to plasma volume)
    - Not a lipophilic drug
  - Metabolism: Hepatic (desulfation, depolymerization)
  - Excretion: Urine (40% unchanged) [3], [4]

Enoxaparin Pharmacology (cont.)



Enoxaparin Pharmacology (cont.)

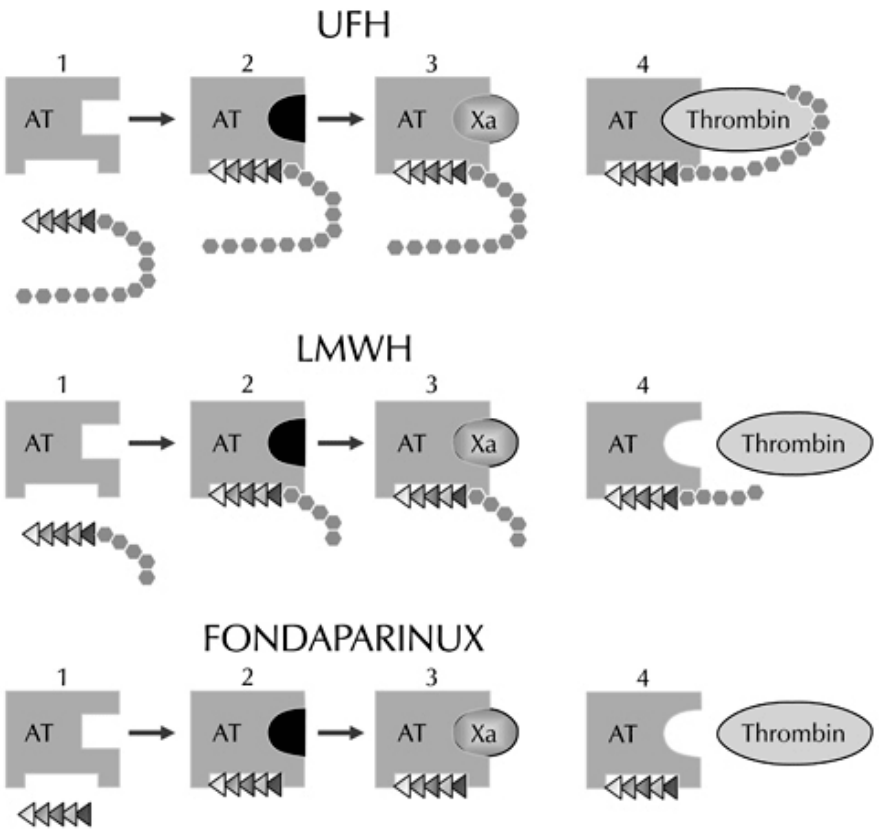


Figure 11-1. Mechanism of action of UFH, LMWH, and fondaparinux. Abbreviations: UFH = unfractionated heparin; LMWH = low molecular weight heparin; AT = antithrombin; Xa = activated factor X.

http://www.ashp.org/s_ashp/docs/files/bookstore/figure11-1.gif

Current Standard Enoxaparin Dosing

- DVT/PE Prophylaxis: 30mg SQ bid **OR** 40mg SQ q daily
  - CrCl ≤ 30ml/min: 30mg SQ qd
- DVT/PE Treatment: 1mg/kg SQ bid **OR** 1.5mg/kg SQ q daily
  - CrCl ≤ 30ml/min: 1mg/kg SQ bid [4], [5]
- Maximum Dose: 150mg SQ bid (per CCF guidelines)

Enoxaparin Dose Monitoring

- Not usually needed unless:
  - Pt is obese
  - Pt has severe renal insufficiency [5]

- Anti-Factor Xa Levels
  - Measured 4 hours post 3rd or 4th dose
  - Goal ranges:
    - 0.2 – 0.4 units/ml (prophylaxis)
    - 0.6 – 1.0 units/ml (BID dosing, treatment)
    - 1-2 units/ml (Q Daily dosing, treatment) [5]

Enoxaparin Dosing Controversy

- Which weight to use for DVT/PE treatment dosing in obese patients?
  - Should the dose be capped?

Dosing Weight Calculation Review

- TBW: Total body weight, in kg
- IBW: Ideal body weight
  - Men: 50kg + (2.3 x height in inches over 60")
  - Women: 45.5kg + (2.3 x height in inches over 60")
- ABW: Adjusted body weight
  - IBW + 0.4(TBW - IBW)
- LBW: Lean body weight (James formula) [7]
  - Men: (1.10 x Weight(kg)) - 128 x ($Weight^2/(100 \times Height(m))^2$)
  - Women: (1.07 x Weight(kg)) - 148 x ($Weight^2/(100 \times Height(m))^2$)

Dosing Weight Calculation Review

- Patient Case:
  - TBW: 186.4kg
  - IBW: 61.6kg
  - ABW: 111.5kg
  - LBW: 82.98kg

Enoxaparin DVT/PE Tx Dose in Obesity

- Enoxaparin distributes to the intravascular space
  - Vd closely tied to plasma volume
    - More dependant on IBW/LBW than TBW [9], [10], [11], [12]
- However, there is no cumulative anticoagulation effect with uncapped dosing
  - Obese patients up to 159kg dosed by TBW [13]
- Inverse correlation between anti-factor Xa levels and body weight
  - Obese pts might may not have proper anti-Xa levels [14]

Development of a dosing strategy for enoxaparin in obese patients [15]

- 96 patients stratified by weight to 3 groups
  - BMI < 25 (32) , BMI 25-29.9 (31) , BMI ≥ 30 (33)
- Tx = enoxaparin 1mg/kg (TBW) SQ bid for ACS/ DVT OR enoxaparin 40mg SQ q daily for prophylaxis
- Separated into 2 further groups after tx
  - Bruising present (26) / bruising not present (70)

Development of a dosing strategy for enoxaparin in obese patients [15]

- Results:
  - BMI difference: p = 0.14
  - Weight difference: p = 0.632
  - CrCl difference: p = 0.01*
- Conclusion:
  - No difference by weight/BMI in patients dosed similarly on enoxaparin
  - Bleeding events tied more to CrCl than weight

Low-molecular weight heparins in renal impairment and obesity: available evidence and clinical practice recommendations [16]

- Expert review article covering 21 studies in the use of LMWH in DVT/PE treatment
- Examined obesity's effects on pharmacokinetic/ dynamics of LMWH in obese
- Created a set of recommendations for enoxaparin dosing in obese patients [16]

Studies used by Nutescu et al in LMWH DVT/PE Dosing Recommendations

EA Nutescu et al.

Table 6b. Pharmacodynamic and Clinical Studies on Use of Treatment Doses of LMWH in Obese Patients

Study	LMWH (or comparator)	n/N[a]	Dosing	Study Design	Definition of Obese	Outcome	Nonobese	Obese
Pharmacodynamic outcomes						**Anti-Xa levels**		
Smith (2003)[84]	dalteparin	21	196.5 units/kg once daily 126.2 units/kg q12h	retrospective open-label	>90 kg	mean		0.9 SD ± 1.1 1.1 SD ± 0.23
Yee (2000)[85]	dalteparin	10/20	200 IU/kg/day or 120 IU/kg q12h	pharmacodynamic	BMI ≥30 kg/m^2	volume of distribution	8.36 (n = 10)	12.36 (n = 10; p = 0.11 vs nonobese)
Wilson (2001)[72]	dalteparin	37	200 IU/kg once daily	prospective cohort	100–120% ideal body weight 120–140% ideal body weight >140% ideal body weight	mean		1.01 (95% CI 0.89 to 1.13) (n = 13) 0.97 (95% CI 0.85 to 1.09) (n = 14) 1.12 (95% CI 0.96 to 1.28) (n = 10)
Sanderink (2002)[86]	enoxaparin	24/48	1.5 mg/kg sc once daily	pharmacodynamic	BMI 30–40 kg/m^2		(n = 24)	14–19% higher vs nonobese (n = 24; p < 0.05)
Bazinet (2005)[32]	enoxaparin	81/233	1.5 mg/kg once daily 1 mg/kg bid	prospective open-label	BMI >30 kg/m^2	mean	1.13 (95% CI 1.04 to 1.22) 1.12 (95% CI 1.03 to 1.20)	1.15 (95% CI 1.02 to 1.28) 1.17 (95% CI 1.08 to 1.25)
Hainer (2002)[87]	tinzaparin	35 37	175 IU/kg 75 IU/kg	pharmacodynamic	100–160 kg	mean	0.87 (95% CI 0.78 to 0.96) 0.30 (95% CI 0.28 to 0.32)	0.81 (95% CI 0.76 to 0.86) 0.34 (95% CI 0.303 to 0.375)
Barrett (2001)[48]	tinzaparin	NA/425	175 IU/kg once daily	data analysis of 2 RCTs	BMI >30 kg/m^2	LMWH clearance		22% decrease

[16]

Clinical outcomes								
VTE treatment						**VTE or major bleeding**		
Al-Yaseen (2005)[88]	dalteparin	193	200 IU/kg once daily	retrospective chart review	>90 kg kg/m^2	recurrent VTE		1.6% (95% CI 0.2 to 5.8)
			100 IU/kg q12h			major bleeding		0.8% (95% CI 0.02 to 4.5)
						recurrent VTE		1.4% (95% CI 0.03 to 7.6)
						major bleeding		1.4% (95% CI 0.03 to 7.6)
Merli (2001)[10]	enoxaparin	900	1 mg/kg once daily	RCT	men: BMI >26.9 kg/m^2,	recurrent VTE	4.4%	7.3%
			1.5 mg/kg q12h		women: BMI >27.2 kg/m^2		2.9%	3.4%
	UFH		adjusted				4.1%	2.5%
RIETE registry Barba (2005)[89]	NA	294/ 8845	different doses	registry analysis	>100 kg	recurrent VTE	1.0%	0.7% (OR 0.7; 95% CI 0.2 to 2.7 vs nonobese)
						major bleeding	1.3%	1.0% (OR 0.8; 95% CI 0.2 to 2.5 vs nonobese)
ACS						**Ischemic events or major bleeding**		
Klein (1997)[15]	dalteparin	NA/ 1482	days 1–6: 120 IU/kg q12h days 7–45: 7500 IU once daily	RCT subgroup analysis	BMI >26	death, MI, UR	15.7%	8.4%
	placebo						13.3%	11.4%
FRISC FRISC Investi-gators (1996)[13]	dalteparin	731/ 1497	120 IU/kg q12h (10,000 IU cap)	RCT subgroup analysis	BMI >26	death, MI	0.8%	2.5%
	placebo						5.5%	4.0%
Spinler (2003)[24]	enoxaparin	921/ 3516	1 mg/kg q12h	RCT subgroup analysis	BMI ≥30	death, MI, UR	16.1%	14.3%
						major bleeding	1.6%	0.4%
	UFH	918/ 3481	adjusted doses			death, MI, UR	19.2%	18.0%
						major bleeding	1.0%	1.2%
	enoxaparin/ UFH					death, MI, UR	16.2%	17.6% (p = 0.39 vs nonobese)
						major bleeding	0.8%	1.3% (p = 0.12 vs nonobese)

ACS = acute coronary syndromes; BMI = body mass index; LMWH = low-molecular-weight heparin; MI = myocardial infarction; NA = not available; OR = odds ratio; RCT = randomized clinical trial; UFH = unfractionated heparin; UR = urgent revascularization; VTE = venous thromboembolism.

[a]n/N = obese patients/total study population. If the total study population included only obese patients, just 1 number is given.

Enoxaparin Dosing Recommendations based on Nutescu et al. Article

- Monitoring not needed in obese pts unless:
  - Weight ≥ 190kg
  - Adjust dose in these patients based on anti-factor Xa
- Only use BID dosing in obese patients
- Created a dosing nomogram based on anti-factor Xa levels [16]

Anti-Factor Xa Based Enoxaparin Dose Adjustment

Table 8. Sample LMWH Dosing Nomogram for Treatment Doses of Enoxaparin

Anti-Xa Level (U/mL)	Hold Next Dose	Dosage Change	Next Anti-Xa Level
<0.35	no	increase by 25%	4 h after next dose
0.35–0.49	no	increase by 10%	4 h after next dose
0.5–1.0	no	no	next day, then in 1 wk, then monthly
1.1–1.5	no	decrease by 20%	before next dose
1.6–2.0	3 h	decrease by 30%	before next dose and 4 h after next dose
>2.0	until anti-Xa <0.5 U/mL	decrease by 40%	before next dose and q12h until anti-Xa <0.5 U/mL

LMWH = low-molecular-weight heparin.

Reproduced from Monagle et al. *Chest* 2001;119(suppl 1):344-70, with permission from the American College of Chest Physicians,[117] adapted according to Nutescu et al.[2]

[16]

Patient Case Follow-Up

- 09/07/10: Pt given enoxaparin 150mg SQ bid
  - Delay d/t insurance coverage issues with dose
- Anti-factor Xa measured 6hrs after 1st dose
  - Anti-factor Xa was 0.3 units/ml (within-range)
- 09/07/10: D/c'd home on enoxaparin bridge to warfarin and PO bactrim after cellulitis resolution
- F/u on enoxaparin completed over phone by CCF pharmaceutical care clinic (PCC)

Conclusions

- Use standard bid enoxaparin dosing in obese patients based on TBW for DVT/PE tx
  - Data only exists on enoxaparin up to 150kg
    - Maximum dose of 150mg/kg
- Monitor anti-factor Xa levels in pts who are morbidly obese (BMI ≥ 40)
  - Adjust dose based on anti-factor Xa level

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