A rationale for the routine monitoring of anti-Xa concentration during enoxaparin treatment

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Introduction

- Enoxaparin is a low molecular weight heparin (LMWH) used in the treatment of thrombotic diseases.
- Treatment with enoxaparin can be monitored by measuring plasma anti-Xa activity.
- There is a perceived lack of need for routine monitoring. In contrast, unfractionated heparin (UFH) treatment is routinely monitored.

Objectives

- To identify a target anti-Xa concentration for treatment with enoxaparin.
- To determine whether routine monitoring of anti-Xa concentrations is warranted.

Treatment Targets

Enoxaprin

- Effectiveness target:
  - Anti-Xa ‹ 500 IU/L at 5 hours post-dose was associated with a 3-fold increase in mortality. (1)
- Safety target:
  - Anti-Xa of 580 IU/L at trough would halve the risk of bleeding. (Ref 2 and Fig 1)
- Target: Peak › 500 IU/L and trough ‹ 500 IU/L

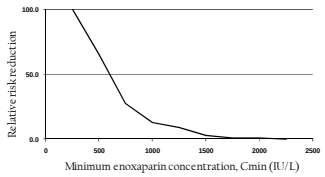

Fig 1: Relative risk of bleeding versus enoxaparin Cmin

Unfractionated heparin (UFH)

- Effectiveness and safety target:
  - 1.5-2.5 x control aPTT
  - Control aPTT (26-36 seconds)

Models

Enoxaparin model (4,5)

- Two-compartment
- Parameters: CL, Q, V2, V3, Ka
- Demographic covariates: ht, wt, Scr
- Derived covariates: LBW, CLcr

UFH model (3)

- One-compartment Michaelis-Menten
- PD model:

aPTT=aPTT0 * exp(M) * Conc where M is the slope of Conc vs. aPTT curve

Simulations

Enoxaparin

- 10 000 virtual patients were simulated with a dosing regimen of 1 mg/kg of total body weight twice daily. Patients with creatinine clearance less than 30 mL/min were excluded. Fig 2

UFH

- Activated partial thromboplastin times (aPTTs) for 10 000 virtual patients were simulated assuming a Michaelis-Menten PK model with an empirical PD model linking concentration to aPTT. No feedback process on aPTT was included. Fig 3

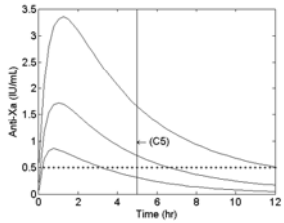

Fig 2: Enoxaparin target. The middle profile fulfils the target criteria (peak is › 500 IU/L and trough is ‹ 500 IU/L)

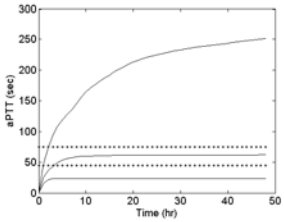

Fig 3: UFH target. The middle profile fulfils the target criteria (aPTT within 1.5-2.5 of the baseline value)

Achieving Treatment Targets

Enoxaparin

- The target was achieved in 54% of patients during the course of treatment (with 23% over target and 23% under target).

UFH

- The target was achieved in 48% of patients at steady state (with 26% over target and 26% under target).

Conclusions

- UFH treatment is monitored routinely (using aPTT) albeit with limited success.
- Enoxaparin has a similar probability of reaching therapeutic target to UFH (54% vs 48%).
- Routine monitoring of anti-Xa with enoxaparin would seem warranted.
- This recommendation could be applied to all LMWHs.

References

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(4) Green B. et al. Br J Pharmacol 2003; 56(1):96-103 (5) Green B. et al. Br J Pharmacol 2005; 59(3):281-90